Cancer Research in Switzerland

A publication of the Swiss Cancer Research foundation,
the Swiss Cancer League and the cantonal cancer leagues
on their funded research projects 2012
Edition 2013

Imprint

Publisher and information:
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Publication date: November 2013

Edition English: 350 Ex.
Edition German: 4900 Ex.
Edition French: 1550 Ex.

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Cover page photo: This photo shows a set of violin strings, made of gut, stranded steel or synthetic materials, wound with aluminum or plated with silver. The editors kindly thank the music stores Jecklin & Co. AG, Zurich and Musikpunkt Lohri AG, Blasinstrumente & Percussion, Lucerne as well as the fishery Fischerei A. Gerny GmbH, Zurich for their support.
Design: Atelier Richner, Visuelle Gestaltung, Bern
www.atelierrichner.ch
Print: Ast & Fischer AG, Wabern

This edition of the report "Cancer Research in Switzerland" and also the 2012, 2011, 2009, 2006 and 2004 editions can be downloaded as PDF files at: www.swisscancer.ch/researchreport

This publication is also available in German and French at:
www.swisscancer.ch/research

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Pia Zanetti's photographs are represented in public and private collections in Switzerland and abroad and have been purchased by the Swiss Confederation and the Swiss Foundation of Photography.

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Cancer Research in Switzerland

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With funding of 20 million Swiss francs, the Swiss Cancer Research foundation, the Swiss Cancer League, and the cantonal and regional cancer leagues invested another new record sum in academic cancer research in 2013. More than 80 per cent of the funds were granted to independent research projects. These are promising research studies in all disciplines of oncology, where research aims and implementation are investigator-initiated, which means they are based on the researchers' ideas.

The research funding in the past years shows clearly that in the funding area "independent research projects", more and more researchers are applying for the limited available funds. Competition has become stiffer, which is fundamentally beneficial to the quality of the funded research studies. But there is another side to competition as well: Recently, there has been an increase in the number of grant applications that are deemed high quality by the Scientific Committee but cannot be funded due to limited financial means. Understandably, for the researchers affected this leads to disappointment.

The good news is that thanks to an increase in charitable donations, the available funds have doubled in the last 15 years. However, over the same period the amount of funding applied for by grant applicants has nearly tripled. One consequence of this is a decrease in the monetary success rate, the amount of funding awarded relative to the amount of funding applied for, which is currently 31 per cent.

Thomas Cerny

Jakob R. Passweg

The board of the Swiss Cancer Research foundation and the board of the Swiss Cancer League have responded to this development. In response to the increasing workload for the review of the grant applications, the Scientific Committee has been enlarged from 15 to 17 members. In addition, the maximum funds granted per research project as well as the maximum number of ongoing supported projects per researcher have been reduced, so that more research projects can be supported. But the top priority of the partner organizations remains unchanged: Only the highest-quality cancer research projects are funded.

This sixth edition of the report "Cancer Research in Switzerland" presents the aims of the research projects approved for funding in 2012 and the results of research projects completed last year. Once again, we extend heartfelt thanks to all of the charitable donors for their loyalty and generosity. A big thank you goes to all of the researchers for their tireless efforts in the service of cancer research and the fight against cancer. Last but not least, we are grateful to all of the people who worked on this edition of the report.

Prof. Thomas Cerny, MD
President of the Swiss Cancer Research foundation

Prof. Jakob R. Passweg, MD
President of the Swiss Cancer League

20 million francs

for outstanding cancer research

In 2012 a total of 20.2 million francs was granted to academic cancer research in Switzerland. The Swiss Cancer Research foundation (SCR) and the Swiss Cancer League (SCL) provided a new record sum of 17.1 million francs, and the cantonal and regional cancer leagues (CCL) gave 3.1 million francs. All of our generous charitable donors deserve our sincerest thanks.

For over 20 years the SCR, SCL, and some CCL have been the leading non-profit organizations funding oncological research at Swiss universities, hospitals, and academic research institutions. The SCR is dedicated exclusively to research funding, and the SCL and the CCL are engaged broadly in the fight against cancer through their central priorities of cancer prevention, early detection of cancer, supporting and advising persons with cancer and their families, and funding cancer research.

Cancer in Switzerland

A cancer diagnosis is a life-altering and distressing event for patients and their families. Each year there are about 37,000 new cases of cancer in Switzerland, and about 16,000 persons die of the disease. On average more than one in three people in Switzerland will develop some form of cancer in their lifetime, and cancer accounts for approximately 25 % of all deaths. In the group under the age of 75 years, cancer is the most frequent cause of death.

Thanks to advances in early detection, diagnosis, and treatment, more than half of the number of patients with cancer can be cured today. That means that they survive longer than five years after cancer diagnosis and some for more than 10 or even 20 years. In addition, many cases of cancer that cannot be cured can be controlled and managed for long periods of time (cancer as a chronic condition). According to extrapolations based on several cantonal cancer registries, at present there are almost 300,000 people living in Switzerland who were or are in treatment for cancer – which is more than double the number of 20 years ago (Figure 1). As life expectancy in Switzerland continues to rise and more than half of cancer cases affect persons older than age 65, the number of these cancer survivors will continue to increase.

Hope thanks to research

Cancer research is one of the greatest hopes in the fight against cancer. The immense worldwide efforts in biomedical science and developments in oncology aim to improve the survival rates and quality of life of persons with cancer. The progress achieved in individual research projects and studies is usually small, but if we look at the path of these many small steps over a time period of one or two decades, the successes become clearly visible. An important focus of the SCR, SCL, and the CCL is also targeted funding of projects that aim to deliver direct benefits for patients – in other words, patient-centred research.

Rolf Marti, PhD
Head of the Scientific Office, Swiss Cancer League, and director of the Swiss Cancer Research foundation, Bern

Funding goes to the entire broad range of cancer research. *Basic biomedical research,* mostly based on laboratory experiments, aims to increase our understanding of molecular and cellular processes that lead to development, proliferation, and spread of cancer cells in the body. *Clinical research* works with patients and aims, for example, to optimize existing treatments, and it also studies cancer cells and tumour tissue from patients, seeking new biomarkers and specific targets so that diagnostic methods can be refined and targeted medications can be developed.

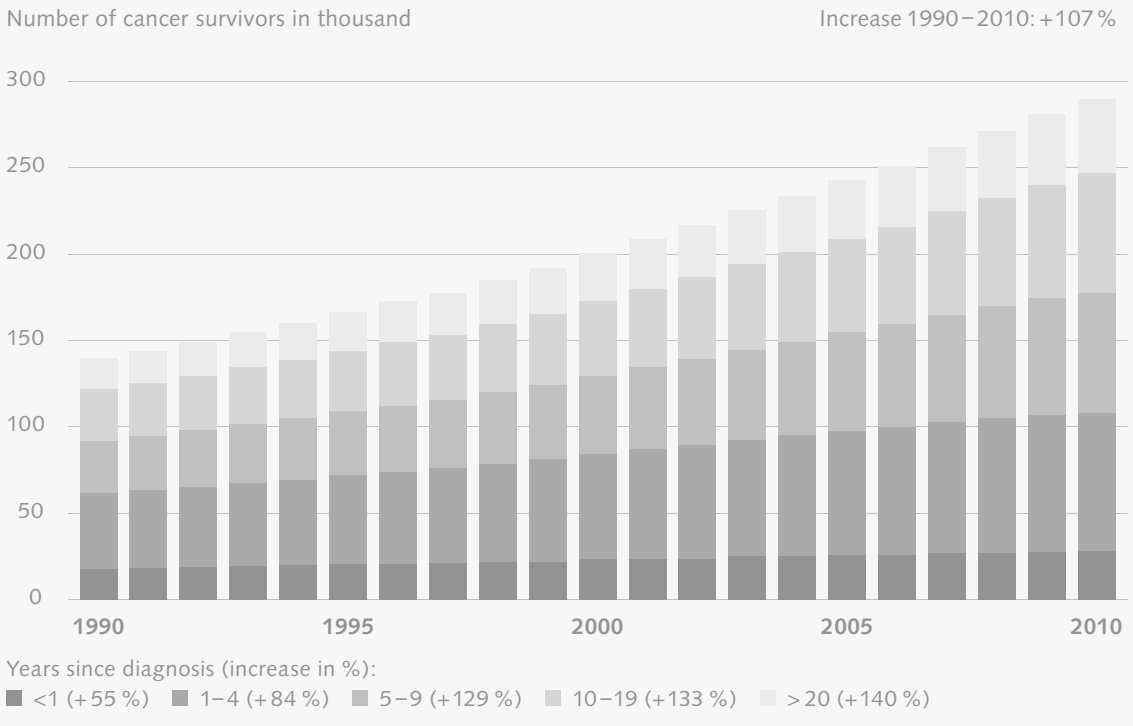
Psychosocial research studies the psychological and social effects of cancer with the aim to improve the quality of life of persons with cancer and their families. *Epidemiological research* examines, for example, the rates of cancers in the population and the factors that have an effect on cancer risk. Also funded are research projects in nursing sciences, prevention, public health, and health services research and outcomes research (research on the quality, effectiveness, and cost control of medical care).

A well-coordinated team

The most important criterion for the selection of research projects for funding is and remains the excellent quality of the research grant application submitted. Fulfilment of the demand for quality is ensured by the Scientific Committee, which together with further international specialists evaluates all grant applications according to strict and clearly defined criteria. The members of the Scientific Committee are recognized experts with outstanding achievements and profound expertise in all areas relevant to oncological research.

The Scientific Office is the competence centre and operational hub for the research funding. The office organizes the call for grant applications and the entire review process, and handles budgetary and quality control of the supported research projects. The Scientific Committee and the Scientific Office work for both the SCR and the SCL. Thanks to this combining of forces, administrative costs are kept low, there is valuable transfer of know-how, and charitable contributions are utilized efficiently.

Figure 1
Estimated number of persons living in Switzerland ever diagnosed with cancer (cancer survivors), 1990–2010
(all invasive cancers, no non-melanoma skin cancers)



Source: Herrmann C, Cerny T, et al. Cancer survivors in Switzerland: a rapidly growing population to care for. *BMC Cancer.* 2013;13:287.

Record sum for research funding

2012 was again a record year for the SCR and the SCL. Together the two organizations provided 16.8 million francs for cancer research. A total of 72 research projects, bursaries, and research organizations were supported (Figure 2). This represents an increase of nearly 3 % over the previous year. Not included in these figures are contributions made to conferences, workshops, and international organizations. In addition to this, the CCL supported a total of 53 research projects and institutions, mainly in their cantons and regions, with a total of 3.1 million francs in funding.

Including funding for other projects, total spending of the SCR and SCL on research funding was 16.7 million francs in 2012 (Table 1). As in previous years, 80 % of the funds came from the SCR and 20 % from the SCL. Together with the funds contributed by the CCL, in 2012 the funding organizations thus contributed 20.2 million francs to academic cancer research.

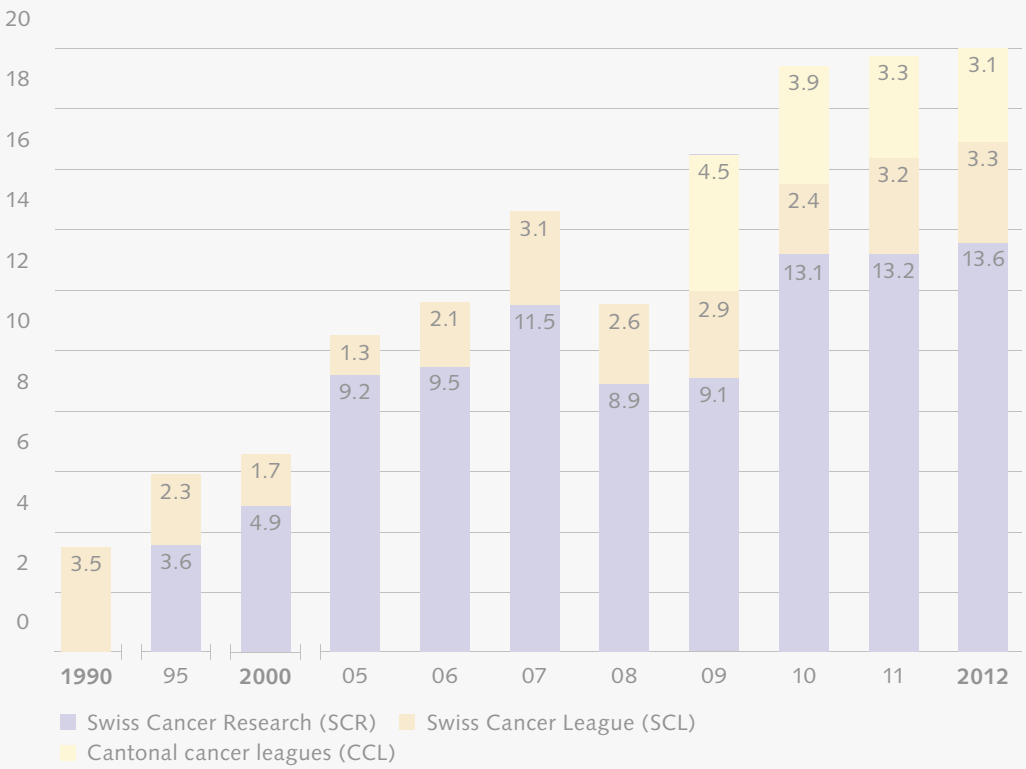
Distribution of cancer research spending

Independent research is and remains the most important focus of research funding by the SCR and the SCL. In 2012 most of the funding – 83 % – went to *independent research projects;* 10 % was given to six Swiss *research organizations* as contributions for basic services; 5 % went to persons receiving *bursaries;* and 2 % went to *other projects,* such as funds for scientific meetings, conferences, and workshops and contributions to international organization like the EORTC Charitable Trust, the foundation for the European Organisation for Research and Treatment of Cancer.

Compared to the previous year, in 2012 the per cent allocation of the research funding to these four funding areas remained quite constant. But looking at the absolute figures, there were some changes in the year-to-year comparison: The biggest increase was in funding going to research organizations, which received just under 17 % (250,000 francs) more funding than in 2011. The funding for bursaries increased

Figure 2

Cancer research funding by SCR, SCL and the CCL (independent research projects, bursaries, programme research, research organizations) since the founding of SCR in 1990. Not included in these figures are funds for other projects (conferences, workshops, etc.). Research funding by the CCL has been recorded centrally and published in this report only since 2009.



by 14 % (114,000 francs) compared to 2011. The funding for other projects decreased by about 25 % compared to the previous year. The funding for independent research projects was 14.2 million francs and thus about the same as in 2011 (14.1 million francs).

Figure 3 shows the distribution of funds by the SCR and SCL to the most important institutions in the cantons. At 86 %, the majority of the funds went to universities and university hospitals in Lausanne, Zurich, Basel, and Bern. Compared to 2011, there were changes in the funding given to the following cantons: Lausanne + 4 %, Zurich −16 %, Basel + 50 %, and Bern + 26 %. A large part of the funding given to Bern was not for independent research projects but rather for four research organizations, whose coordination centre is located in the federal city. The remaining 14 % of the funding in 2012 went to the cantons of Geneva, Ticino, St. Gallen, Aargau, Lucerne, and Fribourg.

Competition in independent research projects

The funding available for independent research projects remained constant, but competition among researchers for the limited funds increased (Table 2). A total of 170 grant applications were submitted to the Scientific Office in 2012, which is one-third more than in 2011. 72 grant applications were submitted in February 2012 and 98 in August. These figures are apparently not statistical outliers and may indicate a new trend, for in February 2013 the Scientific Office received 94 grant applications.

Of the 170 grant applications submitted, the foundation board of the SCR and the board of the SCL funded 66 research projects for a total of 14.2 million francs. Relative to the number of grant applications submitted, this is a grant approval success rate of only 39 %, which is considerably lower than the nearly 50 % grant approval success rate of 2011. The monetary grant success rate, the amount of funds granted relative to the amount of funds requested, decreased from 43 % in 2011 to 31 % in 2012. The reasons for

Table 1
Research funding by SCR and SCL in overview

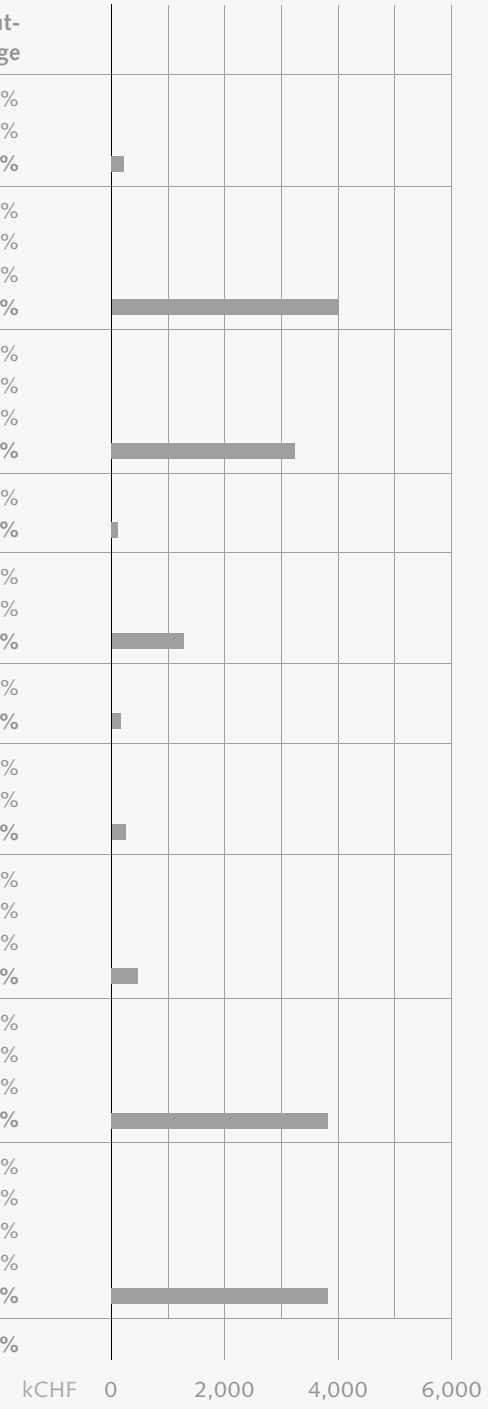
Number of grant applications and amount applied for; number of grants and amounts granted in 2012 (all funding areas)

	Independent research projects	Bursaries	Research organizations	Other*	**Total**
SCR					
Number of grants approved	51	8	6	8	**73**
Amount granted in kCHF	10,998	821	1,760	195	**13,774**
Proportion of total funding	80 %	6 %	13 %	1 %	**100 %**
SCL					
Number of grants approved	15	2	0	14	**31**
Amount granted in kCHF	3,165	97	0	70	**3,332**
Proportion of total funding	95 %	3 %	0 %	2 %	**100 %**
Total SCR and SCL					
Number of grant applications	170	12	6	22	**210**
Number of grants approved	66	10	6	22	**104**
Amount applied for in kCHF	46,110	1,207	1,760	265	**49,342**
Amount granted in kCHF	14,163	918	1,760	265	**17,106**
Proportion of total funding	83 %	5 %	10 %	2 %	**100 %**

* Funding for scientific conferences, workshops, international organizations

Figure 3
Distribution of cancer research funding to the cantons by SCR and SCL in 2012

Canton		Number of projects	Amount in kCHF	Percentage
AG	PSI/Cantonal Hospital	3	213	98 %
	Awards	1	5	2 %
	Total	**4**	**218**	**1 %**
BE	SAKK/IBCSG/SPOG/SCCR	6	1,694	42 %
	University/University Hospital	12	2,316	57 %
	Bursaries	1	57	1 %
	Total	**19**	**4,067**	**23 %**
BS	FMI	5	1,046	32 %
	University/University Hospital	11	2,144	66 %
	Bursaries	1	47	2 %
	Total	**17**	**3,237**	**19 %**
FR	University	1	110	100 %
	Total	**1**	**110**	**1 %**
GE	University/HUG	7	1,267	100 %
	Awards	1	5	0 %
	Total	**8**	**1,272**	**7 %**
LU	Cantonal Hospital	1	155	100 %
	Total	**1**	**155**	**1 %**
SG	Cantonal Hospital	1	186	76 %
	Bursaries	1	59	24 %
	Total	**2**	**245**	**1 %**
TI	IELSG	1	200	42 %
	IOSI/IRB	3	235	50 %
	Bursaries	1	39	8 %
	Total	**5**	**474**	**3 %**
VD	EPFL	8	1,647	43 %
	University/CHUV	8	1,660	44 %
	Bursaries+research awards	5	509	13 %
	Total	**21**	**3,816**	**22 %**
ZH	NICER	1	200	5 %
	ETHZ	4	480	13 %
	University/University Hospital	17	2,817	74 %
	Bursaries	3	318	8 %
	Total	**25**	**3,815**	**22 %**
	Total	**103**	**17,409**	**100 %**



Abbreviations

AG PSI = Paul Scherrer Institute
BE SAKK = Swiss Group for Clinical Cancer Research
IBCSG = International Breast Cancer Study Group
SPOG = Swiss Paediatric Oncology Group
SCCR = Swiss Childhood Cancer Registry
BS FMI = Friedrich Miescher Institute
GE HUG = Geneva University Hospital
TI IELSG = International Extranodal Lymphoma Study Group
IOSI = Oncology Institute of Southern Switzerland
IRB = Institute for Research in Biomedicine
VD EPFL = Swiss Federal Institute of Technology Lausanne
CHUV = Lausanne University Hospital
ZH NICER = National Institute for Cancer Epidemiology and Registration
ETHZ = Swiss Federal Institute of Technology Zurich

Table 2
Distribution of funds by SCR and SCL for independent research projects

	2011	2012	Change compared to prior year
Basic biomedical research			
Number of grant applications	69	87	+26 %
Amount applied for in kCHF	19,061	25,241	+32 %
Percentage of requested funds	58 %	55 %	−3 %
Number of grants approved	29	31	+7 %
Amount granted in kCHF	7,559	7,190	−5 %
Percentage of granted funds	54 %	51 %	−3 %
Grant application number success rate	42 %	36 %	−6 %
Monetary grant success rate	40 %	29 %	−11 %
Clinical research			
Number of grant applications	39	58	+49 %
Amount applied for in kCHF	9,793	14,920	+52 %
Percentage of requested funds	30 %	32 %	+2 %
Number of grants approved	21	20	−5 %
Amount granted in kCHF	4,556	4,146	−9 %
Percentage of granted funds	32 %	29 %	−3 %
Grant application number success rate	54 %	34 %	−20 %
Monetary grant success rate	47 %	28 %	−19 %
Psychosocial research			
Number of grant applications	10	12	+20 %
Amount applied for in kCHF	1,953	2,727	+40 %
Percentage of requested funds	6 %	6 %	0 %
Number of grants approved	6	5	−17 %
Amount granted in kCHF	931	693	−26 %
Percentage of granted funds	7 %	5 %	−2 %
Grant application number success rate	60 %	42 %	−18 %
Monetary grant success rate	48 %	25 %	−23 %
Epidemiological research			
Number of grant applications	9	13	+44 %
Amount applied for in kCHF	1,822	3,222	+77 %
Percentage of requested funds	6 %	7 %	+1 %
Number of grants approved	7	10	+43 %
Amount granted in kCHF	1,034	2,134	+106 %
Percentage of granted funds	7 %	15 %	+8 %
Grant application number success rate	78 %	77 %	−1 %
Monetary grant success rate	57 %	66 %	+9 %
All projects			
Number of grant applications	127	170	+34 %
Amount applied for in kCHF	32,629	46,110	+41 %
Number of grants approved	63	66	+5 %
Amount granted in kCHF	14,080	14,163	+1 %
Grant application number success rate	50 %	39 %	−11 %
Monetary grant success rate	43 %	31 %	−12 %

(percentage of funds)

the enormous increase in the number of grant applications submitted are not yet known. But the effects of this increase are very clear, including the greatly increased workload of the members of the Scientific Committee: Whereas in 2011 the Scientific Committee members each reviewed on average 17 research grant applications, in 2012 this number rose to 23. For this reason, the decision was made to increase the number of members of the Scientific Committee from 15 to 17.

12 **Development of the success rates**

In 2012, the largest part (51 %) of the funds for independent research projects again went to basic biomedical research. In this area of research the competition for funding was also the greatest (Table 2). The monetary grant success rate in 2012 was 29 % (in 2011: 40 %). 29 % of the funding went to clinical research, which encompasses research studies with patients and laboratory research with human biological material (such as translational research). In this area of research the monetary grant success rate decreased to 28 % in 2012 (in 2011: 47 %).

In 2012 15 % of the funding went to epidemiological research, which was more than double the funding in the previous year. Here the monetary grant success rate rose to 66 % (in 2011: 57 %). In contrast, 5 % of the funding went to psychosocial research, and the monetary grant success rate dropped to 25 % (in 2011: 48 %). In these two areas of research the yearly fluctuations in the success rates are due mainly to the relatively small number of grant applications that are submitted and approved. Looking at the number of approved grant applications compared to the number of submitted grant applications, we find the following grant success rates: 36 % for basic biomedical research, 34 % for clinical research, 42 % for psychosocial research, and 77 % for epidemiological research.

Good projects that could not be funded

With an enormous increase in the number of grant applications submitted and approximately the same amount of funds available, it is obvious that grant success rates will go down. But this development of the success rates is problematic, especially when it comes to projects that are approved but not funded (ABNF). These are grant applications that the Scientific Committee deemed high quality and approved for funding but that the boards of the SCR and SCL could not fund due to lack of monies. In 2011 the number of ABNF projects was 15, all of them in the area of basic biomedical research. In 2012 that num-

Table 3
Distribution of funds by SCR and SCL for independent research projects by research area and year, 2003–2012

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Basic biomedical research										
Total in million CHF	4.75	6.00	4.18	5.14	6.12	4.35	4.80	7.00	7.56	7.19
Percentage of total amount	65 %	56 %	49 %	52 %	56 %	48 %	47 %	59 %	54 %	51 %
Clinical research										
Total in million CHF	2.19	3.31	3.36	3.31	3.85	2.90	3.96	3.14	4.56	4.15
Percentage of total amount	30 %	31 %	40 %	34 %	35 %	32 %	39 %	26 %	32 %	29 %
Psychosocial research										
Total in million CHF	0.14	1.00	0.61	0.74	1.05	0.84	0.70	0.36	0.93	0.69
Percentage of total amount	2 %	9 %	7 %	7 %	9 %	9 %	7 %	3 %	7 %	5 %
Epidemiological research										
Total in million CHF	0.22	0.37	0.31	0.74	0.00	0.93	0.74	1.40	1.03	2.13
Percentage of total amount	3 %	4 %	4 %	7 %	0 %	11 %	7 %	12 %	7 %	15 %
All projects										
Total in million CHF	7.30	10.68	8.46	9.93	11.02	9.02	10.20	11.90	14.08	14.16

ber doubled. Of the 33 ABNF grant applications in 2012, 21 were in basic biomedical research and 12 were in clinical research. In the areas of psychosocial and epidemiological research, all projects approved for funding by the Scientific Committee were funded.

Faced with the enormous increase in the number of grant applications in general (+34 %) and in the number of high quality ABNF grant applications (+120 %) the foundation board of the SCR and the board of the SCL decided to take action. According to a new guideline, a researcher may be the principal applicant of at most one ongoing research project (and a co-applicant on two other projects), and the amount granted per application is maximum 250,000 francs (previously, 350,000 francs). The boards hope that these measures will ease the problem to some extent. Whether these changes in the grant guidelines will remain in effect permanently will be decided in the foreseeable future after an evaluation has been conducted.

There was a positive development in fundraising activities with selected foundations that contribute some or all of the costs of research projects that were quality-tested by the Scientific Committee. In 2012, approximately 1 million francs was provided to cancer research in this way. Neither the donors nor the foundations have any influence on the selection of and the aims of the research projects. The projects are selected by the Scientific Committee, and the researchers alone are responsible for the content of their projects.

A focus on patient-centred research

The most important selection criterion in all areas of research is the quality of the projects. In addition, an important priority of the SCR and the SCL is funding patient-centred research. Patient-centred research can be, for example, treatment optimization studies in clinical research that aim to find the optimal sequence and combination of treatment options for

treatment success, or psychosocial research studies that aim to improve the quality of life of persons with cancer and their family members. Nursing research, health services research and outcomes research, and epidemiological research also mostly aim at direct benefits to patients and their families.

The following allocation rules are utilized to increase the funding of patient-centred research: Within the funding area of independent research projects, 60 % of the funding is earmarked for patient-centred research, broken down into 40 % for clinical research and 20 % for research studies in the psychosocial area, nursing sciences, epidemiology, and so on. The remaining 40 % of the funding for independent research projects goes to basic biomedical research. In 2012, the funds were allocated as follows: basic biomedical research 51 %, clinical research 29 %, psychosocial and epidemiological research 20 %. The distribution of funds for independent research projects over the last 10 years has levelled off at somewhat more than 50 % for basic biomedical research and somewhat less than 50 % for patient-centred research (clinical, psychosocial, epidemiological).

Supported research organizations

In 2009 the SCR began to give established Swiss research organizations funds for basic services that these organizations perform for the benefit of translational, clinical, and epidemiological research in Switzerland. Clinical research especially is so costly in terms of time and resources that without external human resources and financial support, it would often be too much for individual hospitals or research institutions to conduct clinical studies.

The services provided by research organizations, such as designing study protocols, coordinating multicentre and international studies, and administrative tasks for the study approval process with Swissmedic and the ethics committees, are immensely valuable for clinical cancer research. Also in the area of cancer epidemiology, researchers depend on the know-how and resources for collecting, managing, and analysing data in the cantonal and national cancer registries. Thus, the funding given to these research organizations is an additional way to promote patient-centred research.

Table 4
Supported research organizations

Funding by SCR according to performance agreement by research organization and year, 2009–2012

Amount in kCHF

	2009	2010	2011	2012
IBCSG	560	560	560	560
IELSG	120*	120*	120*	200
NICER	–	–	200	200
SAKK	600	600	600	600
SCCR	–	–	50	50
SENDO	80*	80*	–	–
SPOG	100	100	100	150
Total	**1,460**	**1,460**	**1,630**	**1,760**

Abbreviations

IBCSG International Breast Cancer Study Group
IELSG International Extranodal Lymphoma Study Group
NICER National Institute for Cancer Epidemiology and Registration
SAKK Swiss Group for Clinical Cancer Research
SCCR Swiss Childhood Cancer Registry
SENDO South European New Drug Organisation (integrated into SAKK since 2011)
SPOG Swiss Paediatric Oncology Group

*former SCR programme "International Clinical Cancer Research Groups" (ICP)

Funds for clearly defined services

On the part of the SCR a maximum of 2 million francs, or at most 20 % of the yearly research funding budget, is reserved for this funding instrument. The monies are not distributed indiscriminately but rather in a targeted way to five or six important research organizations that have conducted or supported cancer research for years. Their basic services are funded based on performance agreements that link the annual funding to clear research targets and reporting and evaluation duties.

The purpose of the contributions from the SCR is to support this indispensable and central work. The condition is that the organizations must secure their financing long-term on their own and independently of these contributions. In 2012 the SCR supported the following research organizations with a total of 1.8 million francs (Table 4 and brief presentation on pages 16/17): Swiss Group for Clinical Cancer Research (SAKK): 600,000 francs, International Breast Cancer Study Group (IBCSG): 560,000 francs, National Institute for Cancer Epidemiology and Registration (NICER): 200,000 francs, International Extranodal Lymphoma Study Group (IELSG): 200,000 francs, Swiss Paediatric Oncology Group (SPOG): 150,000 francs, Swiss Childhood Cancer Registry (SCCR): 50,000 francs.

Research funding by the cantonal cancer leagues

The CCL also supported a considerable number of research projects and institutions in 2012 – mainly in their cantons (Table 5). A total of 3.1 million francs was given to 53 research projects and institutions, including some cantonal cancer registries. The number of projects funded remained practically unchanged in 2012, but again there was less funding: 5 % less than in 2011. Since funding research is not a central objective of most of the CCL, with other tasks increasingly taking priority, the work of the SCR foundation and the SCL are all the more important.

Notable are the extraordinary financial contributions of the Geneva Cancer League, which provided over 1.1 million francs of support (36 % of the total funding from the CCL for research), which is more than double the funding given by the Zurich Cancer League, which provided less than 0.6 million francs (17 %), and the Bern Cancer League, which gave nearly 0.5 million francs (16 %) to research. The remaining 31 % was from the eight cancer leagues of Basel, Ticino, Neuchâtel, Eastern Switzerland, Central Switzerland, Aargau, Thurgau, and Grisons. The remaining eight cantons did not fund cancer research in 2012. The projects and institutions supported by the CCL are presented from page 36.

Table 5
Research funding by the cantonal cancer leagues in overview

Number of research projects and institutions supported and amount granted in 2012 compared to prior year 2011

Cancer league	Number of projects and institutions supported 2011	Number of projects and institutions supported 2012	Change compared to 2011 (absolute)	Amount granted 2011 in kCHF	Amount granted 2012 in kCHF	Change compared to 2011 (relative)
Aargau	3	1	−2	279.5	60.0	−79 %
Basel	7	10	+3	270.0	280.0	+4 %
Bern	8	9	+1	500.1	490.0	−2 %
Central Switzerland	2	2	0	133.0	110.0	−17 %
Eastern Switzerland	0	2	+2	0.0	120.0	–
Geneva	11	12	+1	944.0	1,131.9	+20 %
Grisons	1	1	0	5.0	5.0	0 %
Neuchâtel	1	1	0	124.9	144.0	+15 %
Thurgau	0	2	+2	0.0	33.0	–
Ticino	6	4	−2	290.0	210.0	−28 %
Vaud	1	0	−1	19.4	0.0	–
Zurich	12	9	−3	728.4	551.5	−24 %
Total	**52**	**53**	**+1**	**3,294.3**	**3,135.4**	**−5 %**

The supported research organizations in brief

Swiss Group for Clinical Cancer Research (SAKK)
SAKK is a decentralized academic research institute that has conducted clinical studies on cancer treatment in all larger hospitals in Switzerland since 1965. SAKK encompasses a wide network of about 20 Swiss research groups and a coordination centre in Bern. For rare cancers SAKK works together with selected collaborative groups in other countries. SAKK aims to improve cancer treatment, study the effectiveness and tolerability of new treatments (radiotherapy, chemotherapy, surgery), and establish new treatment standards. In 2012 more than 900 adult patients participated in more than 40 clinical studies conducted by SAKK. As an independent and non-profit organization, SAKK pursues no commercial interests.

International Breast Cancer Study Group (IBCSG)
Since 1977 the IBCSG has conducted academic clinical trials with the aim to support breast cancer research, coordinate international research activities, and improve the treatment of women with breast cancer. The IBCSG is a multicentre study group with a coordination centre located in Bern, a data management centre and a statistics centre in the United States, and a pathology reference laboratory in Italy that serves the entire organization. In Switzerland, all university clinics, numerous cantonal and other hospitals, and oncologists in private practices participate in IBCSG studies. In 2012 just under 1,200 patients participated in clinical studies conducted by the IBCSG.

National Institute for Cancer Epidemiology and Registration (NICER)
NICER aims to improve cancer epidemiology in Switzerland. To this purpose, the NICER foundation coordinates the work of the cantonal and regional cancer registries, compiles and aggregates data, analyses the data at the national level, and makes the data available. The participating cantons at present are Basel Stadt and Land, Fribourg, Geneva, Grisons and Glarus, Jura, Lucerne, Neuchâtel, St. Gallen and Appenzell Ausserrhoden and Appenzell Innerrhoden, Ticino, Valais, Vaud, Zug and Zurich. Aargau and Thurgau will be included starting in 2013/2014 and Bern in 2014/2015. Changes in cancer risk or survival over long periods of time are monitored and quality of care analysed. In addition, epidemiological cancer research is further developed, and education and training in this specialized field is strengthened.

International Extranodal Lymphoma Study Group (IELSG)
The IELSG, a multicentre study group, was created in 1998 in Ascona, and its coordination and data management centre is in Bellinzona. It aims to foster research in the area of extranodal lymphomas (ENL) and to coordinate international research activities. As these lymphomas develop from all organs and sites in the body, different treatments are required, and their effectiveness has to be analysed. To obtain a sufficient number of cases, multicentre studies are necessary. At present there are more than 200 international institutes in this network. The IELSG simultaneously coordinates 10 to 15 clinical studies with the participation of about 350 to 400 patients per year.

Swiss Paediatric Oncology Group (SPOG)
SPOG has been conducting clinical and epidemiological cancer research in paediatric oncology for 35 years. The goal is to improve treatment and quality of life of children and adolescents with cancer and to reduce the occurrence of childhood cancer. The SPOG is a national, independent association located in Bern. Belonging to the SPOG are all paediatric oncology departments at Swiss hospitals, among them those at the five university hospitals, and the Swiss Childhood Cancer Registry. As childhood cancer is relatively rare – in Switzerland there are 180 to 200 new diagnoses per year, research in childhood cancer is possible only in the framework of international collaborations. At present, more than 20 SPOG clinical studies are ongoing, with approximately 125 patients participating.

Swiss Childhood Cancer Registry (SCCR)
The SCCR is the national cancer registry for children and adolescents in Switzerland. It has been in existence since 1976 and collects data on all cancer diagnoses in young persons up to the age of 20. It also documents treatment and conducts longitudinal studies on health and quality of life of childhood cancer survivors. In this way it contributes towards research on the causes of childhood cancer, improvement of cancer treatment, and prevention of late effects in cancer survivors. The SCCR is located at the Institute of Social and Preventive Medicine at the University of Bern and works closely with the SPOG. Up to now, the SCCR – which is funded from several sources – has collected data on 8,700 children and adolescents with cancer.

Evaluation of research funding

For some time now, to ensure that the charitable donations are used as responsibly and profitably as possible, research funding by the SCR and the SCL have been under evaluation by a specialized external firm. The evaluation is based mainly on three methods: (1) bibliometric analysis, to assess the scientific publications produced by the funded research projects quantitatively and qualitatively, (2) a qualitative survey of more than 450 researchers who submitted grant applications in the last five years, and (3) a one-day on-site visit at the Scientific Office by selected international experts. For transparency, the evaluation findings will soon be made available to the public, and a summary of the results will be published in the next *Cancer Research in Switzerland* report.

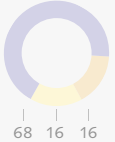
Table 6
Research funding by SCR, SCL, and the CCL in overview

Number of grants approved and amount granted in 2012 and change compared to prior year 2011 (all funding areas)

	Independent research projects		Bursaries		Research organizations		Other*		**Total**	
SCR										
Number of grants approved	51	+6 %	8	+33 %	6	+20 %	8	+100 %	**73**	+16 %
Amount granted in kCHF	10,998	+1 %	821	+9 %	1,760	+8 %	195	+20 %	**13,774**	+3 %
SCL										
Number of grants approved	15	0 %	2	+100 %	–	–	14	−33 %	**31**	−16 %
Amount granted in kCHF	3,165	+1 %	97	+80 %	–	–	70	−63 %	**3,332**	−1 %
CCL										
Number of grants approved	53	+2 %	–	–	–	–	–	–	**53**	+2 %
Amount granted in kCHF	3,135	−5 %	–	–	–	–	–	–	**3,135**	−5 %
Total SCR, SCL and CCL										
Number of grants approved	119	+3 %	10	+43 %	6	+20 %	22	−12 %	**157**	+3 %
Amount granted in kCHF	17,298	0 %	918	+14 %	1,760	+8 %	265	−25 %	**20,241**	+1 %

Change compared to 2011

* Funding for scientific conferences, workshops, and international organizations



(percentage of funds)

Overview of research funding in 2012

Overall, research funding by the SCR, SCL, and the CCL was slightly higher in 2012 than in the previous year: The SCR, SCL, and CCL supported a total of 157 research projects, bursaries, research organizations and institutions, and other projects, providing 20.2 million francs, which was 1 % more than in 2011 (Table 6). This small increase is solely attributable to the SCR foundation, which increased its funding in 2012, whereas the SCL and CCL decreased their funding. The SCR contributed more than two-thirds of the monies, with the SCL and CCL contributing just under one-sixth each. These once again very good results were made possible by the generous and loyal support of our many charitable donors. In the name of all of the organizations, to them we extend our sincere thanks.

Rolf Marti, PhD
Rolf Marti has headed the Scientific Office since 2003 and is responsible for research funding. He is a member of the managing board of the Swiss Cancer League and director of the Swiss Cancer Research foundation. As the person responsible for the platform "Research", the implementation of the National Cancer Programme for Switzerland 2011– 2015 is one of the focuses of his work.
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Partner organizations and committees

Swiss Cancer Research foundation (SCR)

In existence since 1990, the Swiss Cancer Research foundation generates donations that help provide funding for all areas of cancer research: basic, clinical, epidemiological, and psychosocial research. A special focus is the funding of patient-centred research projects that result as far as possible in direct patient benefit. The SCR foundation board, presided over by Prof. Thomas Cerny, MD, is responsible for distributing the funds to the researchers. The funding decisions are based on the recommendations made by the Scientific Committee. The Scientific Committee, made up of recognized experts in cancer research and medicine, reviews the grant applications according to clearly defined criteria. The SCR also supports the development and implementation of measures to fight cancer in Switzerland – namely, the National Cancer Programme 2011–2015.

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Swiss Cancer League (SCL)

The Swiss Cancer League works towards the following aims: fewer people being diagnosed with cancer, fewer people dying of cancer, more people with cancer treated successfully, and providing care and support to persons with cancer and their families in all phases of the disease and in dying. As the national umbrella organization, it brings together 19 cantonal and regional cancer leagues in Switzerland and the Principality of Liechtenstein. The SCL was founded in 1910 and has its headquarter in Bern. Responsible for strategic management is the SCL board, presided over by Prof. Jakob R. Passweg, MD. The SCL is a non-profit organization that is financed mainly through donations. Among its most important tasks are supporting persons with cancer and their families, cancer prevention and early detection, and the funding of cancer research. Another special focus is the education and training of medical specialists.

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Cantonal cancer leagues (CCL)

In the 19 cantonal and regional cancer leagues, persons with cancer and their family members receive personal and individual advice from experts on treatment as well as on financial and organizational questions. The personel at the CCL often advise persons over a longer time period and support them in difficult situations. They provide information on legal and insurance issues and help with the reorganization of the clients' social and financial situations. They provide contacts to other support institutions, such as home care organizations. If their illness brings persons with cancer into financial difficulties, they can apply for support payments. The CCL organize group meetings and courses, where persons with cancer can talk about their fears and experiences and can learn to deal with their illness. Some cancer leagues offer specialized psycho-oncology support for children of adults with cancer. And in some cantons there are outpatient oncology care services that support persons with cancer at home.

The CCL are at work in Switzerland and in Liechtenstein. The services offered by the CCL vary in type and extent and depend strongly on the financial and human resources of the individual cancer league as well as on the services made available by other providers.

Cantonal and regional cancer leagues in the German-speaking part of Switzerland and in Liechtenstein

– Aargau Cancer League
– Basel Cancer League
– Bern Cancer League
– Central Switzerland Cancer League
– Eastern Switzerland Cancer League
– Grisons Cancer League
– Liechtenstein Cancer League
– Schaffhausen Cancer League
– Solothurn Cancer League
– Thurgau Cancer League
– Zug Cancer League
– Zurich Cancer League

Cantonal cancer leagues in the French-speaking part of Switzerland and in Ticino

– Fribourg Cancer League
– Geneva Cancer League
– Jura Cancer League
– Neuchâtel Cancer League
– Ticino Cancer League
– Valais Cancer League
– Vaud Cancer League

The board of the Swiss Cancer Research foundation

The board of the Swiss Cancer Research foundation (SCR) is made up of one representative each of the chairmanship of the Swiss Cancer League (SCL), the Swiss Group for Clinical Cancer Research (SAKK), and the Swiss Paediatric Oncology Group (SPOG); one expert each in the different research areas; and independent persons.

The eight members of the SCR foundation board are:

President

Prof. Thomas Cerny, MD
Head physician of Oncology/ Haematology
Department of Internal Medicine
Cantonal Hospital St. Gallen
Past president of SCL
since 2009

Vice president

Prof. Richard Herrmann, MD
Head of Department of Clinical Research
Basel University Hospital
Past president of SAKK and clinical cancer research representative
since 2009

Prof. Matthias Egger, MD
Director of Institute of Social and Preventive Medicine
University of Bern
Epidemiological cancer research representative
since 2009

Erika Forster-Vannini
Former member of the Council of States
St. Gallen
Independent person
since 2012

Prof. Hans Hengartner, PhD
Langnau am Albis
Basic cancer research representative
since 2009

Eduard Holdener, MD
Therwil
Independent person
since 2009
Treasurer

Gallus Mayer
Banking specialist
Head of Finance and Accounting
Notenstein Private Bank Ltd.
St. Gallen
since 2009

Prof. Nicolas von der Weid, MD
Head of Oncology/Haematology
Co-head physician of Paediatrics
University Children's Hospital Basel (UKBB)
Past president SPOG and paediatric cancer research representative
since 2009

The board of the Swiss Cancer League

The highest body of the Swiss Cancer League (SCL) is the delegates' assembly, to which the representatives of the cantonal and regional cancer leagues belong. Strategic management is the responsibility of the board of the SCL. The members of the board represent both different specialties in the fight against cancer and different parts of Switzerland. Prof. Jakob R. Passweg, MD, was elected president of the board in 2010, and PD Gilbert Bernard Zulian, MD, is vice president.

The 10 members of the SCL board are:

President
Prof. Jakob R. Passweg, MD
Head physician of Haematology
Basel University Hospital
since 2007

Lucienne Bigler-Perrotin
Manager
Geneva Cancer League
since 2009

Vice president
PD Gilbert Bernard Zulian, MD
Head physician of Department
of Palliative Medicine
Hôpital de Bellerive
Geneva University Hospital
since 2009

Treasurer
Gallus Mayer
Banking specialist
Head of Finance and Accounting
Notenstein Private Bank Ltd.
St. Gallen
since 2009

Past president
Prof. Thomas Cerny, MD
Head physician of Oncology/
Haematology
Department of Internal Medicine
Cantonal Hospital St. Gallen
since 1998

Hans Neuenschwander, MD
Head physician of Palliative Care
Regional Hospital of Lugano
since 2010

Irène Bachmann-Mettler
Project head, Institute of General
Practice and Health Services Research
University of Zurich
President of Swiss Oncology
Nursing Society
since 2003

Martin Nobs, lic. phil.
Manager
Bern Cancer League
since 2009

Prof. Daniel Betticher, MD
Head physician of Clinic for Medical
Oncology
HFR Fribourg, Cantonal Hospital
since 2006

Brigitta Wössmer, PhD
Head psychologist of Psychosomatics
Basel University Hospital
President of Swiss Society of
Psycho-Oncology
since 2011

The Scientific Committee

Members of the Scientific Committee 2013 (left to right): Ruth Chiquet Ehrismann (as of 2013), Rolf Marti (head of the Scientific Office), Maria Blettner, Holger Moch, Martin Pruschy, Beat W. Schäfer, Silke Gillessen (as of 2013), Emanuele Zucca (as of 2013), Martin F. Fey (president), Freddy Radtke, Simone Benhamou, Adrian Ochsenbein, Friedrich Stiefel, Hans-Uwe Simon, Jürg Schwaller (as of 2013), Kurt Fritzsche, and Curzio Rüegg (as of 2013) (not pictured: Primo Schär).

The Scientific Committee is responsible for evaluating the research grant applications submitted to the Swiss Cancer Research foundation (SCR) and the Swiss Cancer League (SCL) by researchers seeking research funding. The committee's peer review process uses strictly defined evaluation criteria (see box, "Criteria for high-quality cancer research"). The central criterion is always whether a research project is expected to advance our understanding of cancer prevention, causes, or treatment.

The 15 members of the Scientific Committee are recognized experts with outstanding achievements and expertise in all areas relevant to cancer research. Having all of the research areas represented on one committee prevents the formation of specialized subcommittees and also assures funding of research trends in all areas. The members serve on the committee for three years and can be re-elected twice.

The president of the Scientific Committee is Prof. Martin F. Fey, MD. The committee members are representatives of the following research areas:

- basic biomedical research: 4 members
- patient-centred clinical cancer research: 2 members
- laboratory-based clinical cancer research: 2 members
- epidemiology and cancer prevention: 2 members
- psychosocial and other cancer research (public health research): 2 members
- translational cancer research: 2 members

Each grant application is reviewed by two members of the Scientific Committee. In addition, each application is reviewed by an average of three external peer reviewers. In the year under report, the Scientific Committee reviewed 170 research grant appli-

cations, of which approximately half were in basic research. This represents an increase of 34 per cent in the number of grant applications over the previous year. The workload was correspondingly higher: In 2012 each member of the Scientific Committee reviewed on average 23 grant applications – 25 per cent more than in 2011.

The Scientific Committee meets twice a year to discuss at length the grant applications reviewed by the committee members and external reviewers (see box, "The research grant application review process"). Based on the discussions the committee produces a ranked list of the grant applications that the committee recommends to the boards of the SCR and the SCL for grant approval.

As the financial means are limited, it is unfortunately never possible to approve grants for all grant applications that the committee judges to be of good quality and worthy of funding. In the reporting period 2012 there were 33 research grant applications that could not be approved for funding despite their good quality (these projects are designated "approved but not funded", ABNF), which was more than twice as many as in 2011 (15 ABNF projects).

Operational support for the Scientific Committee's important tasks and responsibility is provided by the Scientific Office of the SCL and the SCR. It organizes the call for and the review of grant applications and is responsible for quality control of the funded research projects.

Criteria for high-quality cancer research

The quality of research grant applications is evaluated according to the following criteria:

- Cancer relevance: Is the proposed research project expected to contribute important new observations or knowledge on the causes, prevention, or treatment of cancer?
- Originality or socio-economic significance: Is the proposed research project original, innovative (basic research projects), or of socio-economic importance (clinical or epidemiological projects)?
- Choice of methodology: Have the most appropriate methods for the project realization been chosen?
- Feasibility: Is the project feasible in terms of finances, human resources, and organization?
- The applicant's past accomplishments: What are the applicant's (or the project group's) previous scientific achievements? How good were the publications?

The research grant application review process

The grant application is submitted to and recorded by the Scientific Office.
↓
The grant application is sent for review to two members of the Scientific Committee who are experts in the relevant specialist field (such as basic research or psycho-oncology).
↓
The two Scientific Committee members recommend additional experts as external reviewers.
↓
The Scientific Office asks the external reviewers to review the grant application.
↓
The reviewers evaluate the grant application. Four to six reviews are obtained for each research grant application, two of which are by Scientific Committee members.
↓
The Scientific Office collects the reviews and puts them in a file.
↓
The research grant application is discussed in detail at the bi-annual meeting of the Scientific Committee.
↓
After the meeting, the Scientific Office writes up detailed minutes and creates a list of all grant applications ranked according to the committee's recommendations.
↓
The ranking list is forwarded to the boards of the Swiss Cancer Research foundation and the Swiss Cancer League, which then decide which grant applications will be funded.
↓
The Scientific Office notifies the applicant of the decision. The reviews are made available to the applicant in an anonymous form.

Members of the Scientific Committee

President

Prof. Martin F. Fey, MD
Institute of Medical Oncology
Bern University Hospital
Bern, Switzerland
since 2006

Prof. Holger Moch, MD
Institute of Surgical Pathology
Zurich University Hospital
Zurich, Switzerland
since 2006

Prof. Simone Benhamou, PhD
Inserm Unit 946 "Variabilité génétique et maladies humaines"
French National Institute of Health and Medical Research (Inserm)
Paris, France
since 2011

Prof. Felix Niggli, MD
Paediatric Oncology
Children's Hospital Zurich
University Children's Clinic
Zurich, Switzerland
since 2002

Prof. Maria Blettner, PhD
Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI)
University Medical Center
Johannes Gutenberg University Mainz
Mainz, Germany
since 2010

Prof. Adrian Ochsenbein, MD
Institute of Medical Oncology
Bern University Hospital
Bern, Switzerland
since 2006

Prof. Gerhard Christofori, PhD
Institute of Biochemistry and Genetics
Department of Biomedicine
University of Basel
Basel, Switzerland
since 2004

Prof. Martin Pruschy, PhD
Department of Radiation Oncology
Zurich University Hospital
Zurich, Switzerland
since 2010

Prof. Kurt Fritzsche, MD
Department of Psychosomatic Medicine and Psychotherapy
Freiburg University Hospital
Freiburg im Breisgau, Germany
since 2009

Prof. Freddy Radtke, PhD
Swiss Institute for Experimental Cancer Research (ISREC)
Swiss Federal Institute of Technology Lausanne (EPFL)
Epalinges, Switzerland
since 2007

Brian A. Hemmings, PhD
Friedrich Miescher Institute for Biomedical Research (FMI)
Basel, Switzerland
2003–2012

Prof. Beat W. Schäfer, PhD
Department of Oncology
Children's Hospital Zurich
University Children's Clinic
Zurich, Switzerland
since 2012

Prof. Primo Schär, PhD
Department of Biomedicine
University of Basel
Basel, Switzerland
since 2010

Prof. Hans-Uwe Simon, MD, PhD
Institute of Pharmacology
University of Bern
Bern, Switzerland
since 2008

Prof. Cristiana Sessa, MD
Oncology Institute of Southern
Switzerland (IOSI)
Hospital San Giovanni
Bellinzona, Switzerland
2000–2012

Prof. Friedrich Stiefel, MD
Liaison Psychiatry Service
Lausanne University Hospital (CHUV)
Lausanne, Switzerland
since 2007

Research awards: Valuable prizes for excellent cancer research

The Swiss Cancer League (SCL) regularly awards the Robert Wenner Award to cancer researchers for excellent research; in 2012 the award was given to Prof. Joerg Huelsken for his research on cancer stem cells. Prof. Roger Stupp was awarded the Cancer Prize for his contributions in research and treatment of brain and lung tumours. The SWISS BRIDGE AWARD was not given in 2012.

Since 1983 the Robert Wenner Award of the SCL has been awarded regularly to cancer researchers under the age of 45 for their excellent research results and highly regarded research papers. This award was endowed by Robert Wenner, a gynaecologist from Basel who died in 1979. The award winners receive 100,000 francs, with 80,000 francs earmarked for an ongoing project and 20,000 francs as discretionary funds. For the researchers, this honour means both recognition of their previous achievements and incentive for future research efforts. As the greater

The Cancer Prize of the Swiss Cancer League 2012

Since 1960 the Swiss Cancer League has awarded the Cancer Prize to recognize excellent contributions to cancer research or outstanding commitment in promoting research activities in the areas of prevention, early detection, and treatment of cancer. The Cancer Prize is also awarded in recognition of services to the Swiss Cancer League and its goals. The prize of 10,000 francs is usually awarded each year.

The Cancer Prize 2012 was awarded to *Prof. Roger Stupp, MD,* for achieving significant advances in the treatment of patients with brain and lung cancer and for his leading role in European cancer research.

Like virtually no other Swiss oncologist Stupp has pursued the goal of linking biological cancer research with medical treatment. At the beginning of this year he was newly appointed director of the Zurich University Hospital cancer centre. He previously headed the multidisciplinary brain tumour clinic at the University of Lausanne Medical Center (CHUV) and was head of the Department of Oncology at the hospitals of Vevey and Monthey. For many years he has initiated and been the lead investigator of large clinical trials at the European level with the aim to improve treatment of patients with malignant brain tumours and advanced lung cancer.

The effectiveness of this strategy – from the laboratory to the hospital bed and from the hospital bed to the laboratory – is evidenced by the improvements in the treatment of glioblastomas: The methods developed under Stupp's leadership have become today's treatment standards internationally. Stupp is also an internationally recognized expert in lung and head and neck cancer. In June 2012, Stupp, who has decisively influenced and advanced clinical cancer research in Europe, was appointed president of the most important clinical cancer research institution in Europe, the European Organisation for Research and Treatment of Cancer (EORTC).

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part of the award money must be invested in cancer research, the award allows the recipients to continue their work or to initiate new projects.

Focus on cancer stem cells

Last November, the *Robert Wenner Award 2012* was given to *Prof. Joerg Huelsken, PhD,* head of the Laboratory for Cancer Stem Cells, at the Swiss Institute for Experimental Cancer Research (ISREC) at the Swiss Federal Institute of Technology Lausanne (EPFL), for his groundbreaking research on cancer stem cells. His research studies have contributed significantly to an understanding of how cancer cells invade and colonize tissues normally inhabited by other cells and spread to form tumours at other sites in the body (metastasis). Using the most advanced research methods in combination with his clear focus on problem solving, Huelsken possesses an impressive track record as an innovative scientist with numerous publications, many in the most prestigious journals.

Our understanding of cancer biology has changed fundamentally in recent years. Today, we know that tumour tissue is not made up of a group of similar cells constantly reproducing themselves, but instead is composed of diverse, hierarchically organized cell types having different functions. A special cell type, which has now been identified in diverse cancers such as blood, brain, breast, colon, prostate, and skin cancer, are cancer stem cells. They are responsible not only for the long-term growth of the tumour and thus for resistance to treatment and relapses but probably also for metastasis formation. Over 80 per cent of cancer deaths are due to these dreaded metastases in other organs of the body.

Prof. Joerg Huelsken, PhD, winner of the Robert Wenner Award 2012

Joerg Huelsken was born in Oberhausen, Germany in 1968. After completing studies in biology and a PhD in molecular biology at Humboldt University in 1998, he conducted post-doctoral research at the Max-Delbrueck Center for Molecular Medicine in Berlin. He joined the Swiss Institute for Experimental Cancer Research (ISREC) in Epalinges in 2003 as associate scientist and project leader for the National Centre of Competence in Research (NCCR) "Molecular Oncology". In 2005 he was nominated Tenure Track Assistant Professor at the EPFL School of Life Sciences. Since 2008 Huelsken holds the Debiopharm Chair in Signal Transduction in Oncogenesis. He was appointed associate professor at the EPFL in 2011 and heads the ISREC Laboratory for Cancer Stem Cells (Huelsken Lab).

Long-term aim: Prevent metastasis

Huelsken and his team are the first to demonstrate cancer stem cells in skin tumours of mice and to block them in animal models. The trick: By preventing the communication of cancer stem cells in their surrounding environment (niche), they were able to stop tumour growth in mice, or cause tumours to completely disappear. Specifically, the researchers blocked β-catenin, an important element in the Wnt signalling pathway, which is especially important in maintenance of skin cancer stem cells.[1]

Recently, Huelsken and his research team achieved another breakthrough with experiments in an animal model: By blocking periostin – an essential protein that enhances Wnt signalling and supports the growth of cancer stem cells – they were able to prevent the cells from forming new metastases in other organs. Here, too, they blocked interaction between the cancer stem cells and their local niche. As a result, the normal cells no longer supported the cancer stem cells in disseminating to and colonizing distant sites. Instead, they disappeared after a few days or remained inactive.[2]

Molecular biologists aim to bring knowledge from the laboratory to the clinic. Should it become possible to target human cancer stem cells efficiently, not only could tumour growth be stopped but also metastasis formation could be prevented. And that would be a milestone in the treatment of cancer.

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Kurt Bodenmüller, lic. phil. nat.
Kurt Bodenmüller is a microbiologist who has worked in the field of science communications since 1997. He worked for many years as a consultant at an international PR company. He has been communications manager at the Scientific Office of the Swiss Cancer League and the Swiss Cancer Research foundation since 2008.
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National Strategy Against Cancer 2014–2017

Fields for action and projects in the area "research"

In the fall of 2011 the Swiss Parliament unanimously forwarded the motion "National Strategy for the Fight Against Cancer: For More Equality of Opportunity and Efficiency". Based on that, Oncosuisse – on behalf of the platform *Dialog Nationale Gesundheitspolitik* and in cooperation with a number of actors and experts – worked out a draft of a National Strategy Against Cancer 2014–2017. It was approved by the federal government and the cantons at the beginning of July 2013. The result of this intensive process and prioritization and grouping of objectives are 15 projects in seven fields for action in the three areas of prevention, care, and research.

The first National Cancer Programme (NCP I) was established at the initiative of Oncosuisse about 10 years ago. Building on that, the second National Cancer Programme 2011–2015 (NCP II) was launched in January 2011, again developed under the guidance of Oncosuisse together with the Swiss cancer organizations and with the support of the federal government and the cantons. The report published in January 2011, which built upon the integrative perspective of NCP I, outlined 10 central fields with over 100 objectives and recommendations for improving the fight against cancer and making it more efficient.

Three goals stand in the foreground: All persons residing in Switzerland have the same right to:

- low cancer risk through prevention and early detection
- appropriate diagnosis and treatment based on the latest findings
- psychosocial and palliative care *(NCP II, p. 5)*.

From the start there was consensus that for the policy-strategic implementation of the NCP II, it would be necessary to prioritize and group objectives, taking into account the limited resources, the structures as they developed in Switzerland, and the projects already ongoing in this field. Three fundamental principles can be derived from the NCP II:

- *Coordination and cooperation:* Optimized cooperation among all areas involved and systematic coordination of the activities planned are important.
- *Integrated care:* Persons with cancer should receive care and support in all phases, so that a high quality of life can be maintained and promoted.
- *Best possible quality and equality of opportunity:* The population should have equal access to early detection, diagnosis, and medical, nursing, psycho-oncological, psychosocial, rehabilitative, and palliative care.

The three areas of prevention, care, and research should be viewed as a complex, whole process. At the same time, a disease-related and resource-oriented perspective should be followed.

Kathrin Kramis-Aebischer, PhD
Managing director of the Swiss Cancer League and responsible for the operational management of the National Cancer Programme 2011–2015 and the Strategy Against Cancer, Bern

From May 2012 to May 2013, under the guidance of Oncosuisse and in a broad process involving numerous organizations and institutions, suggestions for central fields for action and implementation projects for the areas of prevention, care and research were developed. In a framework of broadly based consultations, these suggestions were discussed with experts and prioritized. After the draft was approved, the strategy report was approved by the Swiss Conference of the Cantonal Ministers of Public Health in May 2013 and acknowledged by the Federal Council in July 2013.

In this way, the first National Strategy Against Cancer 2014–2017 was developed. It is broadly anchored, both scientifically/medically and politically. With 15 prioritized projects in seven fields for action for the three areas of cancer prevention, care, and research, the strategy outlines concrete ways to achieve the objectives set by the NCP II. The most important prerequisite is shared, partnership-like commitment on the part of all actors, so that all persons with cancer receive efficient care of the best possible quality.

The fields for action and projects in the area of research were developed by diverse specialists in different disciplines under the platform direction of Rolf Marti, PhD.

Kathrin Kramis-Aebischer, PhD
After working for some years as a primary school teacher and special education teacher, Kathrin Kramis-Aebischer studied clinical psychology and education sciences at the University of Fribourg. She completed a PhD in educational psychology with a PhD dissertation on stress and coping with stress. She trained concurrently as a person-centred psychotherapist (SGGT/SPCP). Over the course of the last 25 years Kramis-Aebischer had acquired a wealth of experience in research, management, and teaching, as well as in organizational consulting and development. Most recently she was the director of the Institute for Further Education at PH Bern University of Teacher Education. She has been managing director of the Swiss Cancer League since 1 September 2011. On behalf of Oncosuisse she is responsible for the operational management of development of the Strategy Against Cancer.
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National Strategy Against Cancer 2014–2017
(Excerpt from the area "research", pages 34–37. Dialog Nationale Gesundheitspolitik (Hrsg.). Bericht «Nationale Strategie gegen Krebs 2014–2017». Bern: Oncosuise; 2013. Verfügbar unter: http://www.nationalegesundheit.ch/de/projekte/nationale-strategie-gegen-krebs-2014-2017/index.html)

The area "research" focuses on two fields for action. In the field for action "promotion of research", the focus is on the research directions that have been less developed up to now. In "epidemiology and monitoring", the focus is on further development of foundations for the recording of full-coverage and uniform data.

Field for action 6: Promotion of research
Research has a very strong position in the area of cancer. In basic biomedical research, Switzerland is even an international leader. However, there are research areas that still have a need for development. This includes non-market-oriented, academic clinical and translational research and research on cross-cutting areas such as palliative care, rehabilitation, psycho-oncology, and health services. Ongoing projects and the activities of various actors in these research areas should therefore be continued.

Objectives:
1) Promote clinical and translational research by means of systematic and coordinated cooperation.
2) Improve the transfer of results from basic research to treatment and clinical research.
3) Strengthen exchange and network building among researchers, especially for research in cross-cutting areas.
4) Build up and strengthen health services research.

Project 6.1: Health services research
In Switzerland health services research is still a new research direction with little institutional support. With the new, integrated approaches in care, there is a need for research that demands a stronger interdisciplinary perspective, includes sociological, economic, and political approaches, and involves accompanying research and evaluation research. The Swiss Academy of Medical Sciences has established a nucleus for health services research, which is to be built up and further developed.

Project aims and measures:

1) Establish and institutionalize health services research.
   - A research committee will be established with the participation of the professional organizations and associations to promote exchange on relevant research issues.
   - A society/association for health services research will be founded.
   - A proposal for a National Research Programme (NRP) on health services research will be written and submitted to the Swiss National Science Foundation (SNSF) in the next evaluation round.

2) Conduct practice-oriented interdisciplinary research
   - In the research work at universities and hospitals, there will be a focus on research topics in public health, health economics, palliative care, and nursing.
   - Cooperation among the researchers at different universities will be strengthened.

3) The Federal Office of Public Health (FOPH) and the Swiss Conference of Cantonal Ministers of Education (EDK) support health services research (including outcome data) in the framework of their jurisdictions as an independent and relevant area of research and utilize the findings in planning.

NCP II objectives: Health services research and outcomes research will be developed (NCP II, pp. 81, 146, 159, 170).

Project 6.2: Clinical and translational research

There is still a need to promote clinical and translational research. Besides the topics studied by the pharmaceutical industry, which are oriented also towards the demands of the market, more research questions pertaining to everyday clinical work, namely, treatment optimization (outcomes research), need to be studied. In addition, translational research should be further strengthened by establishing additional coordinating networks and platforms. Here, there is a need for targeted investigation of issues pertaining to exchange between researchers and clinical users.

Excellent examples in the area of translational research are the coordinating networks and platforms of the National Centre of Competence in Research (NCCR) "Molecular Oncology – From Basic Research to Therapeutic Approaches" (2001–2013), which foster exchange between researchers and clinicians. Playing a special role in strengthening translational research is the Swiss Cancer Centre in Lausanne, which grew out of the NCCR and whose support and governance is jointly provided by Lausanne University Hospital (CHUV), the University of Lausanne, the Swiss Federal Institute of Technology Lausanne (EPFL), and the ISREC foundation.

The task now is to continue the previous and new activities and initiatives and where possible expand them, to create in Switzerland sustainably and firmly anchored, networked, high-quality translational and clinical research with a cross-cutting orientation.

Project aim and measures:

1) Improve the framework conditions in clinical research.
   - The approval and implementation procedures set out in the new law on human research (HFG; entering into force 1 January 2014) will be evaluated.
   - Recommendations for long-term research programmes in oncology will be worked out in the context of NCCR programme calls and NRP rounds and coordinated with the private research funding institutions.
   - Within their respective spheres of competence, hospitals, universities, professional societies, and research funding institutions will create more attractive conditions for research and incentive systems for clinical researchers, with the aim to increase research activities and improve career perspectives.
   - The responsible actors will plan postgraduate training programmes for medical personnel working in research.
   - More patient-centred clinical research projects will be conducted, in particular treatment optimization studies (especially in paediatric oncology).
   - Translational research will be established at the universities (cancer research initiatives in the area of translational research will be supported by transfer platforms).
   - Exchange between researchers in basic biomedical research, translational research, and clinical research will be fostered.
   - Universities, university hospitals, and cantonal hospitals, in cooperation, will implement clinical dissertation programmes for researchers, with a focus on clinical and translational research questions.

NCP II objectives: More findings from basic biomedical research will reach clinical application through the strengthening of translational and clinical research. The framework conditions for clinical cancer research will be improved. This increases research activity and improves career perspectives (NCP II, pp. 81–82).

Field for action 7: Epidemiology and monitoring

Valid data conforming to international guidelines are indispensable for the planning and coordination of a Strategy Against Cancer. The available data in the cancer registries are still not recorded uniformly and with full coverage. For this reason, data registration and data preparation by the national coordination agency – the National Institute for Cancer Epidemiology and Registration (NICER) – will be further developed to allow optimal planning of prevention (for example, screening programmes) and care (for example, treatment quality) and investigation of specific research questions, especially in outcomes research. In paediatric medicine, the Swiss Childhood Cancer Registry has registered data on childhood cancer uniformly and with full coverage for years, including data on treatment, treatment quality, and outcomes.

With the planned federal law on cancer registration, the aim is for a Swiss-wide uniform legal basis for cancer registration.

Objectives:
1) Cancer registration will be structurally anchored and coordinated at the national level.
2) There will be a federal law on the registration of cancer.
3) Education and further education in epidemiology will be further developed.
4) Financing will be secured for data registration and data evaluation.
5) The findings will be prepared and published.
6) It will be possible to link cancer registry data with other databases.

Project 7.1: Federal law on cancer registration (KRG)
The cantonal cancer registries serve the planning, measuring of results, and the coordinating of health policy measures in prevention, care, and research. At present, not all of the cantons have a cancer registry for adults, and the recording of data is not uniform. Currently, a federal law is being developed that aims at Swiss-wide, uniform registration of cancer data under harmonized framework conditions. The law is also meant to ensure that there are data available to serve as a basis for screening programmes and treatment and for evaluation of their effectiveness. The commenting and review of the preliminary draft legislation was completed in the first quarter of 2013.

Project aim and measure:
1) Continue work on the creation of the needed legal bases.
   – The implementation of the federal law on cancer registration will be prepared together with the relevant actors as soon as possible.

NCP II objectives: There will be Swiss-wide, full-coverage, and uniform registration of data of a minimal database in cantonal or regional cancer registries and coordination by a national cancer registry agency (NCP II, p. 23). There is a need for a specific federal law on registration of cancer and other diseases (NCP II, p. 23).

Project 7.2: Registry data on treatment quality and data linking
Due to the different ways today's cantonal cancer registries came into being, the data recorded decentrally are not uniform and do not everywhere meet international standards for a modern, productive registry. In particular, there is a lack of data on treatment quality.

Project aims and measures:
1) Create professional foundations that will allow, once the federal law on cancer registration enters into force, the registry of data on treatment quality.
   – Outcome data on early detection and treatment quality will be recorded.
   – Quality indicators will be compatible with international standards and allow comparisons with other countries.
2) The data recorded will be accessible to the authorities and the public.
   – The data will be available for epidemiological studies and can be linked with other databases.

NCP II objectives: There will be Swiss-wide, full-coverage, and uniform registration of data of a minimal database in cantonal or regional cancer registries and coordination by a national cancer registry agency. Data registration will be high quality and the registration coverage will meet international standards. There will be monitoring of treatment quality and costs in connection with the introduction of the new SwissDRGs (Swiss Diagnosis Related Groups) (NCP II, pp. 24, 146, 159, 170).

Project 7.3: Knowledge transfer in practice and policy
The need for policy-relevant, reliable data is likely to increase in the future. Up to now, the available data have not been sufficiently utilized in policy making, especially care planning. For more effective transfer, better measures are needed. For one, the data must be properly prepared, and for another, the transfer of this data to policy making must be organized. The cancer registry data provide evidence on which to base health policies (prevention, screening programmes) and treatment quality.

Project aim and measure:
1) Policy decision making will be increasingly evidence-based.
   – A platform for information transfer from research to policy will be established.

NCP II objectives: There will be consistent application of epidemiological data as a basis for decision making in cancer prevention and health policy (NCP II, p. 24).

Research funding by the cantonal and regional cancer leagues

There are 19 cantonal and regional cancer leagues and the Swiss Cancer League as the national umbrella and specialized organization. In 2012, 11 cantonal cancer leagues – among them the Zurich Cancer League – gave 3.1 million francs to cancer research projects and institutions. Responsible for distributing the funds is the Cancer Commission of the canton of Zurich, a group of experts made up of an equal number of representatives of the Zurich Cancer League and the canton of Zurich. The commission's work focuses on strengthening research in Zurich .

In 2012 the Zurich Cancer League supported cancer research in the Canton of Zurich with funding of 560,000 francs. Grant applications requesting in total 1,767,750 francs were received. The average funding by the Zurich Cancer League in the last five years was approximately 850,000 francs. These numbers contribute towards strengthening research in the canton of Zurich, the importance of which is underlined by the presence of the Institute of Technology Zurich and the University of Zurich, together with the Zurich University Hospital and the resulting synergies. The high quality of life in Zurich and the surrounding region is also responsible for attracting researches to the area.

The Cancer Commission of the canton of Zurich is responsible for selecting the research projects for funding. To assure the greatest transparency of the selection process and to strictly avoid conflicts of interest, the Zurich Cancer League decided to create an independent cancer commission outside of the League about 25 years ago. As an independent and authorized committee, the commission's task is essentially to advise the Zurich Cancer League in the distribution of their funding for cancer research projects, in the coordination of research activity, and in the representation of cancer research in the canton of Zurich. The government of the canton of Zurich was seen as a logical partner, represented by the Department of Education of that time as the umbrella organization of the university system.

The Cancer Commission of the canton of Zurich was founded officially on 15 March 1978 with the signing of a contract that set out the composition of the commission as follows:

- dean, as the representative of the Faculty of Medicine of the University of Zurich ex officio
- three members delegated by the Government Council of the canton of Zurich, of which two are research experts designated by the Faculty of Medicine and one is a representative of the Department of Education
- three members designated by the Zurich Cancer League, of which one is a delegate of the *Ärztegesellschaft* (medical association) of the canton of Zurich
- a commission president, elected by the government of the Canton of Zurich at the request of the Cancer Commission of the canton of Zurich.

Organization, rights, and obligations of the commission, concrete procedures for the evaluation process and review, and rights and obligations of grant applicants are laid down in regulations and procedural guidelines.

Hans Kaspar Schulthess, MD
President of the Cancer Commission of the canton of Zurich, member of the board of the Zurich Cancer League, medical specialist for gastroenterology and internal medicine, Zurich

The members of the Cancer Commission of the canton of Zurich are:

- Hans Kaspar Schulthess, MD, Zurich, president
- Prof. Bruno Fuchs, MD, PhD, head of Tumour Surgery, Uniklinik Balgrist
- Prof. Klaus W. Grätz, MD, DMD, dean of the Faculty of Medicine, University of Zurich
- Jörg Kehl, head of HR Professors, University of Zurich
- Prof. Holger Moch, MD, director of the Institute of Surgical Pathology, Zurich University Hospital
- Prof. David Nadal, MD, head of Division of Infectious Diseases and Hospital Epidemiology, Children's Hospital Zurich
- Prof. Miklos Pless, MD, head of Medical Oncology, Cantonal Hospital Winterthur,
- Prof. Rolf A. Stahel, MD, senior staff physician, Clinic of Oncology, Zurich University Hospital

The aim of research funding by the cancer leagues is to support non-commercial funding of cancer research in Switzerland, and in this way it has become an important and essential supporting pillar of highly specialized oncological research. The financial means needed come for the most part from donations and bequests from countless, mostly anonymous donors who want to contribute to the fight against cancer. Most donors have no exact idea of what cancer research is and simply hope that their donations will be used sensibly by the cancer leagues and the responsible commissions.

To narrow this knowledge deficit, the Cancer Commission of the canton of Zurich decided three years ago to discontinue the symposium for researchers previously held every four years and to start up annual information symposiums in non-technical language for potential donors and the wider public. The goal is to give symposium attendees an idea of what cancer research is and how a research project is typically conducted: namely, compiling evidence-based knowledge, developing a supposition or hypothesis, testing the hypothesis through data from systematic observation or experiments, drawing conclusions by comparing the hypothesis to the data, and formulating perspectives for future research.

The 2012 symposium, "Promising cancer research projects in the canton of Zurich", was held in collaboration with the Zurich Cancer League. A member of the commission served as moderator, and three researchers gave presentations on their research projects funded by the Zurich Cancer League. They spoke on "Causes of fatigue in persons with cancer", "Tumours are made up of different cells", and "Cancer vaccines, taking the example of stomach cancer". The latter presentation in particular demonstrated well how unexpected research findings can lead to completely new knowledge that can point researchers in a new direction. The symposium audience obviously enjoyed experiencing researchers first hand, asking them questions, and taking a look behind the scenes of their work. The Zurich Cancer League and the Cancer Commission hope that the public will continue to show their wonderful willingness to donate to cancer research thanks to this kind of information event, in spite of the difficult economic climate.

Hans Kaspar Schulthess, MD
Hans Kaspar Schulthess is a medical specialist in gastroenterology and internal medicine and has had a practice in Zurich for over 25 years, with daily contact with cancer patients. He is a long-year member of the board of the Zurich Cancer League and has been president of the Cancer Commission of the canton of Zurich since 2003.
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List of funded research projects, institutions, and programmes in 2012

The list shows the financial contributions granted in 2012.

Aargau Cancer League

Kuehni Claudia E. | CHF 60,000.–
Bereich Internationale Gesundheit und Umwelt und Schweizer Kinderkrebsregister (SKKR), Institut für Sozial- und Präventivmedizin, Universität Bern, Bern
The educational situation in childhood cancer survivors in Switzerland

Basel Cancer League

Bentires-Alj Mohamed | CHF 50,000.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Inhibition of the calcium-activated chloride channel TMEM16A / ANO1 reduces breast cancer growth

Bubendorf Lukas | CHF 15,000.–
Institut für Pathologie, Universitätsspital Basel, Basel
Diagnostic significance of ERG expression in biopsies of early detected prostate cancer

Chiquet-Ehrismann Ruth | CHF 50,000.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
SAP-dependent MKL1 signalling in tumour progression

Hemmings Brian A. | CHF 50,000.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
DNA damage-mediated HSET-dependence in cancer cells and its potential for cancer therapy

Iezzi Giandomenica | CHF 12,500.–
Departement Biomedizin, Universitätsspital Basel, Basel
Phenotypic and functional characterization of tumour-infiltrating and peripheral blood monocyte subsets from patients with colorectal cancer

Kind André B. | CHF 20,000.–
Frauenklinik, Universitätsspital Basel, Basel
Human papillomavirus types in cervical cancer in Malawi – do we have the right vaccine to start immunization?

Mindt Thomas L. | CHF 12,500.–
Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
Novel antagonistic radiopeptide mimetics for the diagnosis and therapy of cancer

Rentsch Cyrill A. | CHF 15,000.–
Urologische Klinik, Universitätsspital Basel, Basel
New markers for treatment response to radiotherapy in prostate cancer

Sommer Gregor | CHF 5000.–
Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
Assessment of treatment response in patients with metastatic neuroendocrine carcinoma under metabolic radionuclide therapy with ^{90}Y-DOTATOC using diffusion- and perfusion-weighted magnetic resonance imaging

Tzankov Alexandar | CHF 50,000.–
Institut für Pathologie, Universitätsspital Basel, Basel
Clonal relationship of relapsing lymphomas

Bern Cancer League

Gautschi Oliver | CHF 59,000.–
Medizinische Onkologie, Luzerner Kantonsspital, Luzern
SAKK 19/09: bevacizumab, pemetrexed and cisplatin, or erlotinib and bevacizumab for advanced non-squamous NSCLC stratified by EGFR mutation status. A multicentre phase II trial including biopsy at progression (BIO-PRO trial)

Karamitopoulou-Diamantis Eva | CHF 70,000.–
Institut für Pathologie, Universität Bern, Bern
Role of microRNAs and PTEN/PI3K/AKT pathway in pancreatic cancer progression from localized to metastatic disease: relationship to tumour budding, prognosis and response to adjuvant therapy

Novak Urban | CHF 75,000.–
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
Whole-exome sequencing of aggressive mediastinal lymphomas in two female siblings

Pabst Thomas | CHF 50,000.–
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
Randomized evaluation of vinorelbine versus gemcitabine for mobilization of peripheral stem cells in myeloma patients undergoing autologous stem cell transplantation

Reyes Mauricio | CHF 30,000.–
Institut für Chirurgische Technologien und Biomechanik (ISTB), Universität Bern, Bern
Medical image analysis for brain tumour studies

Saurer Leslie | CHF 45,000.–
Institut für Pathologie, Universität Bern, Bern
Significance of triggering receptor expressed on myeloid cells-1 (TREM-1) in experimental colorectal cancer (CRC) development and its role as prognostic marker in human CRC

Schardt Julian | CHF 30,000.–
Institut für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
Investigating the combined cytotoxic effect of the Cox-2 inhibitor celecoxib and the proteasome inhibitor bortezomib in leukaemic cells

Schmitt Kurrer Anja Maria | CHF 76,000.–
Institut für Pathologie, Universität Bern, Bern
The role of angiogenesis and hypoxia signalling in the response prediction to targeted therapy of pancreatic neuroendocrine tumours pNET

von Gunten Stephan | CHF 55,000.–
Institut für Pharmakologie, Universität Bern, Bern
Siglec-7 and Siglec-9 receptors on NK cells: expression and function in cancer

Central Switzerland Cancer League

Diebold Joachim | CHF 50,000.–
Zentralschweizer Krebsregister, Luzerner Kantonsspital, Luzern
Do the new possibilities for targeted therapy lead to an improvement in survival rates of advanced lung cancer patients in central Switzerland?

Heinimann Karl | CHF 60,000.–
Forschungsgruppe Humangenetik, Universität Basel, Basel
Comprehensive genetic analysis of Lynch syndrome colorectal cancers by exome-wide sequencing

Eastern Switzerland Cancer League

Böhm Steffen | CHF 20,000.–
Centre for Cancer & Inflammation, Queen Mary University, London, United Kingdom
Interleukin-6 in high-grade serous ovarian cancer

Ludewig Burkhard | CHF 100,000.–
Institut für Immunbiologie, Kantonsspital St. Gallen, St. Gallen
Systems biology approach to molecularly characterize the lung cancer microenvironment

Geneva Cancer League

Ansari Marc | CHF 80,000.–
Département de pédiatrie, Hôpitaux universitaires de Genève (HUG), Genève
Pharmacogenomics of childhood cancer

Clement-Schatlo Virginie | CHF 200,000.–
Service de neurochirurgie, Département des neurosciences cliniques, Hôpitaux universitaires de Genève (HUG), Genève
The biology of cancer-initiating cells

Cohen Marie | CHF 109,168.–
Département de gynécologie et d'obstétrique, Hôpitaux universitaires de Genève (HUG), Genève
Novel therapeutic approaches against ovarian cancer recurrence

Dietrich Pierre-Yves | CHF 135,000.–
Service d'oncologie, Département de médecine interne, Hôpitaux universitaires de Genève (HUG), Genève
Identification and validation of glioma antigens: towards immunotherapies for brain tumours

Irminger Irmgard | CHF 50,000.–
Département de gynécologie et d'obstétrique, Hôpitaux universitaires de Genève (HUG), Genève
Regulation of the oncogenic isoforms of the tumour suppressor BARD1 in cancer by microRNAs and non-coding RNAs

Kruithof Egbert | CHF 50,000.–
Faculté de médecine, Hôpitaux universitaires de Genève (HUG), Genève
Epigenetic regulation of tissue factor and plasminogen activator in acute promyelocytic leukaemia cells

Mandriota Stefano | CHF 25,000.–
Département de pédiatrie, Division d'onco-hématologie, Hôpitaux universitaires de Genève (HUG), Genève
Assessment of the carcinogenicity of aluminium chloride in human mammary gland epithelial cells

Mandriota Stefano | CHF 100,230.–
Département de pédiatrie, Division d'onco-hématologie, Hôpitaux universitaires de Genève (HUG), Genève
The ATM/p53 signalling pathway in the regulation of cellular senescence

Reith Walter | CHF 111,159.–
Département de pathologie et d'immunologie, Faculté de médecine, Université de Genève, Genève
Identifying the cellular functions and regulatory networks that underlie the link between microRNA-155 and cancer

Thore Stéphane | CHF 90,000.–
Département de biologie moléculaire, Faculté des sciences, Université de Genève, Genève
Steroid receptor RNA activator: a new target for modulating the hormonal response in cancer cells

Tille Jean-Christophe | CHF 70,000.–
Département de pathologie clinique, Faculté de médecine, Université de Genève, Genève
Role of heparan sulfate in endometrioid carcinoma: tissue remodelling, angiogenesis and lymphangiogenesis

Zaïdi Habib | CHF 111,337.–
Département de radiologie, Faculté de médecine, Université de Genève, Genève
Multitracer molecular imaging of tumour metabolism, cell proliferation and hypoxia: a pathway to personalized targeted therapy

Grisons Cancer League

von Moos Roger | CHF 5,000.–
Medizinische Onkologie und Hämatologie, Kantonsspital Graubünden, Chur
Patient management study: telephone follow-up regarding new symptoms during treatment with oral fluoropyrimidine

Neuchâtel Cancer League

Registre neuchâtelois des tumeurs | CHF 144,037.–
Registre neuchâtelois des tumeurs, Neuchâtel
Contribution to the cancer registry

Thurgau Cancer League

Kodex-Stiftung | CHF 3,000.–
Kodex-Stiftung für Suchtmittel-Prävention, Frauenfeld
Contribution to the Kodex programme

Krebsregister Thurgau | CHF 30,000.–
Thurgauische Stiftung für Wissenschaft und Forschung, Frauenfeld
Contribution to the cancer registry

Ticino Cancer League (Fondazione ticinese per la ricerca sul cancro)

Bertoni Francesco | CHF 80,000.–
Laboratorio di oncologia sperimentale, Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
The methylome of splenic marginal zone lymphoma: an integration of epigenetic, genetic and clinical data

Frattini Milo | CHF 50,000.–
Istituto cantonale di patologia, Locarno
Investigation of the role of NEU3 in colorectal carcinogenesis and in the prediction of efficacy of EGFR targeted therapies

Grassi Fabio | CHF 40,000.–
Istituto di ricerca in biomedicina (IRB), Bellinzona
Purinergic signalling in the pathophysiology of central nervous system infiltration in T-cell leukaemia

Thelen Markus | CHF 40,000.–
Istituto di ricerca in biomedicina (IRB), Bellinzona
Detailed study of the interactions and subcellular distribution of the tumourigenic chemokine receptor CXCR7/RDC1 in lymphocytes

Zurich Cancer League

Bernasconi Michele | CHF 66,300.–
Experimentelle Infektiologie und Krebsforschung, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Role of proprotein convertases in paediatric sarcomas: useful theragnostic targets?

Bornhauser Beat | CHF 61,300.–
Forschungsgruppe Leukämie/Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Large scale drug response profiling to identify new targets in refractory leukaemia

Cancer Network Zurich | CHF 10,000.–
Universität Zürich, Zürich
Contribution to the 2012 symposium

Dedes Konstantin | CHF 52,880.–
Klinik für Gynäkologie, Universitätsspital Zürich, Zürich
Screening for novel synthetic lethal treatment approaches in endometrial cancer: a drug library based approach

Raineteau Olivier | CHF 70,420.–
Zentrum für Neurowissenschaften Zürich, Universität Zürich und ETH Zürich, Zürich
E proteins as transcriptional targets in experimental gliomas

Renner Christoph | CHF 54,696.–
Klinik und Poliklinik für Onkologie, Medizinbereich Innere Medizin-Onkologie, Universitätsspital Zürich, Zürich
Boosting of NY-ESO-1 specific re-directed T-cells

Riediger Thomas | CHF 57,880.–
Institut für Veterinärphysiologie, Vetsuisse-Fakultät, Universität Zürich, Zürich
Pharmacological inhibition of inflammatory nuclear factor κB signalling as a possible treatment approach against the cancer anorexia/cachexia syndrome

Sartori Alessandro A. | CHF 78,000.–
Institut für Molekulare Krebsforschung, Universität Zürich, Zürich
MicroRNA-mediated repression of CtIP implications for genomic instability and lymphomagenesis

Schäfer Beat | CHF 100,000.–
Abteilung Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Transcriptional repression of PAX3/FOXO1 by fenretinide

Aargau Cancer League

Kuehni Claudia E. | **The educational situation in childhood cancer survivors in Switzerland**
Bereich Internationale Gesundheit und Umwelt und Schweizer Kinderkrebsregister (SKKR), Institut für Sozial- und Präventivmedizin, Universität Bern, Bern
Duration: 01.01.2012 – 31.12.2012

Within the Swiss Childhood Cancer Survivor Study we investigated childhood cancer survivors' school-related problems and well-being compared to siblings. We sent a questionnaire to survivors and siblings (aged 8–20 years) assessing their educational situation. The Swiss Childhood Cancer Registry provided cancer related data. We received 830 questionnaires from survivors and 227 from siblings. Survivors were more likely than siblings to repeat a year in school (23 % vs. 12 %). Most affected were survivors with migration background, brain tumour, bone marrow transplantation, aged 5–10 years at diagnosis and those who had a relapse. School-related quality of life (being happy at school, doing well, and being able to pay attention) did not differ significantly between survivors and siblings. Repeating a year in school is necessary for some survivors. But they feel just as comfortable at school as their siblings.

Basel Cancer League

Bentires-Alj Mohamed | **Inhibition of the calcium-activated chloride channel TMEM16A /ANO1 reduces breast cancer growth**
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Duration: 01.06.2012 – 31.12.2013

The gene encoding the calcium-activated chloride channel TMEM16A /ANO1 maps to 11q13, one of the most frequently amplified chromosomal regions in human neoplasia, including breast cancer. We showed that ANO1 is both amplified and overexpressed in breast cancer and other 11q13-amplified cancers, and that ANO1 is a critical survival factor in these cancers. We showed that ANO1 modulates both EGFR- and Ca^{2+}/calmodulin-dependent protein kinase (CAMK) signalling in breast cancer and HNSCC cells and revealed that both pathways are essential for ANO1's oncogenic activity in 11q13-amplified cancers. Taken together, our results suggest that ANO1 is a critical oncogenic factor contributing to cell survival, proliferation, and tumour maintenance in 11q13-amplified cancers.

Bubendorf Lukas | **Diagnostic significance of ERG expression in biopsies of early detected prostate cancer**
Institut für Pathologie, Universitätsspital Basel, Basel
Duration: 01.06.2012 – 31.05.2013

TMPRSS2-ERG gene fusion is found in 50 % of all prostate cancers and plays an important role in the development of these tumours. It has recently become possible to demonstrate the gene fusion simply and directly by means of immunohistochemistry of tissue sections. We studied the frequency and distribution of ERG expression in punch biopsies from 256 patients with prostate carcinomas detected early. We found ERG gene fusion also in approximately 50 % of these early carcinomas. In 12 % of the 169 patients with two or three affected biopsies, there were cancer foci with different ERG status (positive and negative), which points to two independently developed cancer foci in the same prostate. Future studies will have to investigate whether this clonal tumour heterogeneity has clinical significance with regard to prognosis or treatment planning.

Chiquet-Ehrismann Ruth | **SAP-dependent MKL1 signalling in tumour progression**
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Duration: 01.05.2012 – 31.01.2013

Many cancer patients can be cured as long as their tumour has not spread yet to form distant metastases. However, if metastatic foci have developed in distant organs, a cure becomes difficult, since the metastases can no longer be surgically removed. We found that the extracellular matrix, the substance that ties our cells together, plays an important role in this process. For example, the extracellular matrix protein tenascin-C is highly enriched in tumours, and the higher the content of tenascin-C the more likely the tumour will become invasive and metastasize. Of course, tenascin-C is not the only factor involved, and it is our aim to identify more components affecting the metastatic behaviour of tumour cells. Once identified, this will provide the basis for the development of drugs targeting these pro-metastatic factors to interfere with the process. Our aim is to identify novel metastatic proteins and signalling pathways and to unravel their mechanism of action.

Hemmings Brian A. | **DNA damage-mediated HSET-dependence in cancer cells and its potential for cancer therapy**
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel

Iezzi Giandomenica | **Phenotypic and functional characterization of tumour-infiltrating and peripheral blood monocyte subsets from patients with colorectal cancer**
Departement Biomedizin, Universitätsspital Basel, Basel

Colorectal cancer (CRC) represents the third most common cancer worldwide, with higher prevalence in developed regions. In Switzerland, about 6,000 patients are diagnosed with CRC each year, with a mortality rate of approximately 1,600 deaths in both sexes, which by far exceeds European yearly rates. In CRC clinical practice, surgery in combination with chemotherapy and radiotherapy offers a potential cure, but with a post-treatment survival rate of less than 60 %. In view of these failures, there is a strong need for development of more effective complementary medical treatments for CRC patients. Our research focuses on specific subsets of immune cells, called monocytes that could represent new therapeutic targets of CRC. In particular, we are studying whether the number and phenotype of monocytes circulating in the blood of CRC patients can predict disease progression. Our long-term goal is to identify how monocytes could promote tumour rejection in patients.

Kind André B. | **Human papillomavirus types in cervical cancer in Malawi – do we have the right vaccine to start immunization?**
Frauenklinik, Universitätsspital Basel, Basel

Invasive cervical cancer (ICC) causes a tremendous individual, social, and economic burden. Marked geographical variations in ICC occurrence are known. Recently, vaccines against two human papillomavirus subtypes became available in industrialized countries. These HPV subtypes cause the majority of ICC cases worldwide, but with significant regional differences. For Malawi, which has a high burden of ICC and is one of the poorest countries in the world, as well as for the entire Southern and East African region, there is insufficient data on which HPV subtypes contribute to ICC. As the introduction of subsidized vaccines in developing countries is being considered, the HPV subtype distribution has to be known. We will analyse tissue samples of ICC from Malawian patients for HPV subtypes. The results of this study will allow stakeholders to answer the question as to whether the introduction of HPV vaccination in Southern and East Africa with the available vaccines is reasonable or whether different HPV subtypes have to be included in new vaccines.

Mindt Thomas L. | **Novel antagonistic radiopeptide mimetics for the diagnosis and therapy of cancer**
Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
Duration: 01. 05. 2012 – 31. 12. 2012

Radioactive labelled peptides are being used in the clinic for the diagnosis and therapy of certain types of cancer. A drawback of the peptides employed is their inherent biological instability, often resulting in rapid degradation within minutes. It is known that an enhanced stability of peptidic radiotracers correlates with an increased tumour uptake. Our research program aims at the development of stabilized radiopeptides by the replacement of labile amide bonds with stable synthetic analogues. The novel radiopeptide mimetics should exhibit improved stability while their high affinity towards receptors expressed by tumour cells is retained. In the future, translation of the new radiopharmaceuticals into the clinic for applications in nuclear oncology is envisioned.

Rentsch Cyrill A. | **New markers for treatment response to radiotherapy in prostate cancer**
Urologische Klinik, Universitätsspital Basel, Basel
Duration: 01. 06. 2012 – 31. 12. 2013

The actual follow-up of patients undergoing definite radiotherapy for prostate cancer includes regular measurements of prostate specific antigen (PSA). Successful radiotherapy is critically dependent on local control of cancer; however, PSA takes two to three years to reach a nadir after therapy. We aim at collecting blood/urine after prostate massage before and after radiotherapy in order to define new markers predicting local control earlier and more precisely than PSA. Patients at risk for local relapse may benefit from earlier diagnosis of failure of local control.

Sommer Gregor | **Assessment of treatment response in patients with metastatic neuroendocrine carcinoma under metabolic radionuclide therapy with ^{90}Y-DOTATOC using diffusion- and perfusion-weighted magnetic resonance imaging**
Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
Duration: 01. 10. 2011 – 31. 12. 2013

Through the development of the therapy agents ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC at the end of the 1990s, the Clinic of Nuclear Medicine at Basel University Hospital is the leading centre in Switzerland and one of the largest centres worldwide for treatment of neuroendocrine tumours. The success of a DOTATOC treatment is commonly assessed by measuring the evolution of tumour size in repeated computed tomography (CT) examinations. However, it is a big disadvantage of this method that a definite assessment of response is not possible earlier than three months after finalization of the treatment. This not only means a long time of uncertainty for the patients but also makes it difficult for the therapists to learn the early effects of the treatment. The aim of this study is to demonstrate that diffusion-weighted and perfusion-weighted magnetic resonance imaging (MRI) can predict the success of treatment with ^{90}Y-DOTATOC as early as two days after initiation of the treatment.

Tzankov Alexandar | **Clonal relationship of relapsing lymphomas**
Institut für Pathologie, Universitätsspital Basel, Basel
Duration: 01. 09. 2012 – 31. 12. 2013

Lymphomas are a heterogeneous group of neoplasms, most of which usually respond to treatment. However, a substantial number of patients will have a relapse. In general, lymphoma relapses are considered to represent a more aggressive (treatment-resistant) recurrence of the primary disease, but this concept has been recently challenged. It is now acknowledged that recurrences in some patients might represent a clonally unrelated secondary neoplasm that developed *de novo*. It has been suggested that these patients should not receive aggressive treatment but be treated by standard first-line therapy. We are investigating clonal relationships in relapsing follicular, diffuse large B-cell and classical Hodgkin lymphomas on the molecular level by evaluating genetic aberrations in recurrence and comparing them to the primary disease. Studying large series of samples might also aid determination of unifying genetic lesions that have diagnostic or therapeutic importance.

Bern Cancer League

Gautschi Oliver | **SAKK 19/09: bevacizumab, pemetrexed and cisplatin, or erlotinib and bevacizumab for advanced non-squamous NSCLC stratified by EGFR mutation status. A multicentre phase II trial including biopsy at progression (BIO-PRO trial)**
Medizinische Onkologie, Luzerner Kantonsspital, Luzern
Duration: 01. 04. 2012 – 31. 03. 2014

More than 3,700 patients are diagnosed with lung cancer in Switzerland every year. Lung cancer incidence and mortality are stable in men but rising in women. Patients with early stage lung cancer are offered curative surgery. Unfortunately, over 70 % of patients with lung cancer have metastatic disease at the time of diagnosis. Until recently, chemotherapy was the standard-of-care for those patients. A few years ago, activating mutations in the epidermal growth factor receptor (EGFR) were discovered as predictive markers for targeted therapy. The Swiss Group for Clinical Cancer Research (SAKK) therefore initiated the phase II trial SAKK 19/09. In that trial, patients with tumour harbouring activating EGFR mutations were treated with erlotinib (an EGFR inhibitor) and bevacizumab. Patients without EGFR mutations received platinum-based chemotherapy and bevacizumab. At the time of disease progression, tumour biopsy was repeated for translational research. The current project will analyse tumour and blood samples for biomarkers associated with resistance to the different drugs used in the SAKK 19/09 trial. The main objective is to define markers that aid clinical decision making about the optimal choice of systemic therapy ("personalized medicine").

Karamitopoulou-Diamantis Eva | **Role of microRNAs and PTEN/PI3K/AKT pathway in pancreatic cancer progression from localized to metastatic disease: relationship to tumour budding, prognosis and response to adjuvant therapy**
Institut für Pathologie, Universität Bern, Bern
Duration: 01. 04. 2013 – 31. 03. 2015

Pancreatic cancer has a 5-year survival rate of less than 5 %. Despite our understanding of the molecular alterations during early stages of neoplastic transformation, late molecular events underlying the progression to invasion and metastasis are not understood. Tumour budding (presence of single tumour cells or small cell clusters at the invasive front of carcinomas) occurs frequently in pancreatic cancer and is linked to decreased disease-free and overall survival. The PTEN / PI3K pathway is commonly mutated in cancer. MicroRNAs (a family of small non-coding RNA molecules) regulate gene expression at the post-translational level and act on tumour invasion and metastasis through targeting PTEN. This research project will help to determine the effect of microRNAs and PTEN on therapy resistance of pancreatic cancer, allow us to gain insight into the later stages of pancreatic carcinogenesis, and provide us with a platform leading to the identification of new therapeutic interventions.

Novak Urban | **Whole-exome sequencing of aggressive mediastinal lymphomas in two female siblings**
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
Duration: 01. 06. 2012 – 31. 09. 2013

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma in the adulthood, accounting for about 35 % of lymphomas in Western countries. DLBCL is heterogeneous in terms of morphology, genetic lesions, and clinical features. Three distinct subtypes can be distinguished based on the cell that they originate from. The subtypes are morphologically indistinguishable but harbour distinct clinical behaviours. The current knowledge on genetic lesions in DLBCL was gathered over years through single gene analyses. Recent improvements in sequencing technologies allow investigation of whole genomes for genetic alterations.

Although rare, familial clustering of malignant lymphoma is documented. The understanding of hereditary malignancies is an attractive opportunity to unravel new molecular markers and novel therapeutic targets in a given disease. We have access to a family in which two young sisters (22 and 31 years old) were affected with lymphomas. Previous analyses revealed both different and shared features. An assessment of the complete coding genomic alterations of the lymphomas in these siblings by whole-exome sequencing (WES) is being conducted. The common genetic lesions will be determined, and their frequency will be assessed in different lymphomas.

Pabst Thomas | **Randomized evaluation of vinorelbine versus gemcitabine for mobilization of peripheral stem cells in myeloma patients undergoing autologous stem cell transplantation**
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
Duration: 01.04.2013 – 31.03.2015

Autologous stem cell transplantation is a medical procedure in which stem cells (cells from which other cells of the same type develop) are removed, stored, and later given back to the same person. Combined with high-dose chemotherapy, it is a cornerstone in the current treatment for patients with multiple myeloma below the age of 70 years. This treatment has been shown to significantly prolong overall survival. The chemotherapy used to treat this type of cancer is both well tolerated and efficient in reducing the tumour. However, its main side effect is peripheral neuropathy. Neuropathy is also a frequent side effect of the methods used for collecting the autologous stem cells required for the transplantation. In this project, we aim to compare the standard regimen used to collect the stem cells with a new regimen that does not cause neuropathy. If successful, this would reduce the side effects of the treatment for multiple myeloma.

Reyes Mauricio | **Medical image analysis for brain tumour studies**
Institut für Chirurgische Technologien und Biomechanik (ISTB), Universität Bern, Bern
Duration: 01.04.2013 – 31.03.2015

Brain tumours are rare, but the survival rate is limited. Magnetic resonance imaging (MRI) is the method of choice to non-invasively detect and analyse brain tumours. In clinics, several different MRI modalities are used simultaneously for diagnosis. Currently, radiologists conduct radiologic assessment of tumour response using two-dimensional measurements. A volumetric (3D) tumour assessment would yield a more accurate analysis. However, the lack of reliable tools for volumetric assessment is hindering the progress towards clinical adoption.

Over the last few years we have developed tools for automatic analysis of brain tumour images. The aim of this project is to consolidate previous developments and to bring the tool to the clinics. First, we want to improve accuracy, robustness and speed. Second, we want to make use of the full 3D information. And third, we want to do a thorough evaluation and validation on a large clinical dataset. In addition, this project will explore the potential of the proposed tool for replacing the measurement criteria used currently. This tool will benefit the patient by providing a more accurate and objective interpretation of the disease.

Saurer Leslie | **Significance of triggering receptor expressed on myeloid cells-1 (TREM-1) in experimental colorectal cancer (CRC) development and its role as prognostic marker in human CRC**
Institut für Pathologie, Universität Bern, Bern
Duration: 01.05.2013 – 30.04.2014

Chronic inflammation and tumour progression are tightly linked. Cells and mediators of the innate immune system in particular have been ascribed important roles in amplifying tumour growth. Colitis-associated cancer (CAC) represents a paradigm of inflammation-driven cancer. Our laboratory previously identified a central role for the innate immune amplifier TREM-1 in the pathogenesis of colitis, as blocking TREM-1 significantly attenuates disease. In contrast to blockade of TNF, blocking TREM-1 does not appear to compromise immunity. We speculate that targeting of TREM-1 could represent a novel treatment strategy also in CAC. To address the significance of TREM-1 in the development of CAC, TREM-1-deficient mice will be analysed in an experimental model of CAC. Moreover, to investigate the potential of TREM-1 as novel prognostic marker in human CRC, TREM-1 expression will be systematically assessed on tissue specimens derived from a well-characterized cohort of patients with CRC.

Schardt Julian | **Investigating the combined cytotoxic effect of the Cox-2 inhibitor celecoxib and the proteasome inhibitor bortezomib in leukaemic cells**
Institut für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
Duration: 26.11.2012 – 25.05.2013

Acute myeloid leukaemia (AML) accounts for approximately 80 % of acute leukaemia in adults. AML is mainly a disease of the elderly, with median age 72 at diagnosis. Population-based studies have reported a 5-year survival rate of only 3–8 % in patients over age 60. Therefore, novel treatment strategies are needed.

Conditions that disrupt protein folding in the endoplasmic reticulum (ER), such as nutrient deprivation or chemical insults, activate an intrinsic stress signalling pathway known as the unfolded protein response (UPR) pathway to restore cellular homeostasis. If the homeostatic balance is not re-established, after inducing the UPR, for example through increased expression of protein-folding molecules (chaperones), the cells initiate a terminal UPR and ultimately undergo apoptosis. The retrograde translocation of misfolded proteins from the ER depends on functioning cytosolic proteasomes. Thus, treating cells that have an activated UPR with proteasome inhibitors (PIs) might result in the accumulation of misfolded proteins within the ER and finally induce apoptosis.

In a previous screen we identified the Cox-2 inhibitor Celecoxib as a strong inducer of the UPR in leukaemic cells. Therefore, we plan to test whether pre-treatment of leukaemic cells with the UPR activating agent Celecoxib sensitizes cells to subsequent treatment with a proteasome inhibitor (e. g. bortezomib), which might result in induction of a terminal UPR and apoptosis. The ratio of compounds that exerts the maximal apoptotic effect will be determined, and we hope that in this way these *in vitro* findings can be translated into clinical applications in the near future.

Schmitt Kurrer Anja Maria | **The role of angiogenesis and hypoxia signalling in the response prediction to targeted therapy of pancreatic neuroendocrine tumours pNET**
Institut für Pathologie, Universität Bern, Bern
Duration: 01. 07. 2012 – 30. 06. 2014

Over 50 % of patients with pancreatic endocrine tumours (pNET) suffer from tumour recurrence after surgery and die of their cancer. It is difficult to predict in which patients tumours will recur, and until recently the treatment options for patients with recurrences were very limited. It was recently found that a subset of patients with metastasizing pNET respond to a specific targeted therapy, but it is not possible to predict which patients will respond to this treatment. Our group showed that a subset of sporadic pNET display inactivation of the VHL gene. These tumours are associated with an adverse outcome. The underlying mechanisms are now being dissected on human tissues and cell lines. We intend to define a molecular subgroup of pNET that will respond to a specific targeted therapy and determine how this subtype can be detected. Our results have the potential to have immediate impact on clinical practice.

von Gunten Stephan | **Siglec-7 and Siglec-9 receptors on NK cells: expression and function in cancer**
Institut für Pharmakologie, Universität Bern, Bern
Duration: 01. 04. 2013 – 31. 03. 2014

We are interested in molecular mechanisms that control inflammation and cancer. Natural killer (NK) cells are critical to innate immunity. Members of a novel class of inhibitory receptors on human NK cells, Siglec-7 and Siglec-9, have recently received particular attention in light of their capacity to mediate cell death, anti-proliferative effects, and inhibition of cellular activities. These receptors inter-

act with specific carbohydrates ligands (sialoglycans). We recently found that the ligands are overexpressed on human tumour cell lines of different histological types and in tumour biopsies from melanoma patients. Here, we will further explore the role of Siglec-7 and Siglec-9 and their ligands in tumour immunity and NK cell resistance. The experiments will provide further insights into the role of Siglec receptors in different types of malignancies and might lead to novel diagnostic or prognostic biomarkers and molecular targets for therapeutic intervention in cancer.

Central Switzerland Cancer League

Diebold Joachim | **Do the new possibilities for targeted therapy lead to an improvement in survival rates of advanced lung cancer patients in central Switzerland?**
Zentralschweizer Krebsregister, Luzerner Kantonsspital, Luzern
Duration: 01.01.2011 – 31.12.2013

Based on the numbers from the Cancer Registry of Central Switzerland, we will examine the following questions: In how many patients are the new targeted therapies an option at all? How many patients are effectively treated with the new treatment in question? And will this new therapy lead to an improvement of survival? The correlation of the cancer registry data with the histopathological findings and the genetic analysis will lead to a gain in information that can contribute to the correct application of the new targeted therapies and to a better definition of the prognosis in the individual patient.

Heinimann Karl | **Comprehensive genetic analysis of Lynch syndrome colorectal cancers by exome-wide sequencing**
Forschungsgruppe Humangenetik, Universität Basel, Basel
Duration: 01.01.2011 – 31.12.2012

Lynch syndrome, formerly known as hereditary non-polyposis colorectal cancer, refers to the most commonly inherited cancer predisposition. The disease is characterized by the development of mainly colorectal and endometrial cancers. Identification of genes commonly altered in fresh-frozen colorectal cancer specimens from Lynch syndrome patients with pathogenic MLH1/MSH2 germline alterations will increase knowledge of the genetic alterations leading to colorectal cancer in Lynch syndrome patients and will shed light on intestinal carcinogenesis in general.

Eastern Switzerland Cancer League

Böhm Steffen | **Interleukin-6 in high-grade serous ovarian cancer**
Destination: Centre for Cancer & Inflammation, Queen Mary University, London, United Kingdom
Duration: 01.05.2012 – 30.04.2013

The aim of this project is to improve ways of treating a common form of ovarian cancer. Ovarian cancer, like many other cancers, is not only a mass of malignant cells; about 50 % of the cancer is made up of other "normal" cells that are recruited and corrupted by the cancer cells by sending out chemical signals, especially molecules called cytokines. My host laboratory has shown that one of these cytokines, interleukin-6 (IL-6), is important for the recruitment. The lab has studied drugs that stop IL-6 working, and these have shown some activity in patients with ovarian cancer. However, this approach may work best in patients whose tumours make the highest amounts of IL-6 and in combination with chemotherapy. In my research I will attempt to find a blood test that will allow to estimate how much IL-6 each patient's tumour is making and to find the best ways to combine anti-IL-6 antibody treatment with chemotherapy.

Ludewig Burkhard | **Systems biology approach to molecularly characterize the lung cancer micro-environment**
Institut für Immunbiologie, Kantonsspital St. Gallen, St. Gallen
Duration: 01.01.2012 – 31.12.2015

Tumour cells display distinct genetic alterations that permit their unrestricted growth. In contrast, stromal cells that provide the growth scaffold and nutrients for the tumour most likely exhibit universal signatures that determine their function. The aim of this project is to gain novel knowledge on stromal cells that determine the growth-supporting micro-environment of lung cancer. Researchers at the Cantonal Hospital St. Gallen have developed unique tools and methods to label, characterize and molecularly ablate lung cancer stromal cells. We expect that our research will identify critical target structures on lung cancer stromal cells and that this knowledge will foster the development of novel diagnostic and therapeutic avenues.

Geneva Cancer League

Ansari Marc | **Pharmacogenomics of childhood cancer**
Département de pédiatrie, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2012 – 31.12.2012

Clement-Schatlo Virginie | **The biology of cancer-initiating cells**
Service de neurochirurgie, Département des neurosciences cliniques, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2012 – 31.12.2012

Gliomas are primary brain tumours. They are the most common in men and are among the most aggressive and difficult to treat cancers despite advances in surgery, radiotherapy and chemotherapy. In recent years, it has been shown that several types of cancer, including gliomas, have cancer stem cells that constitute a small subpopulation among tumour cells. These cells can proliferate indefinitely and feed the growth of the tumour while being

resistant to treatment. To fight cancer stem cells specifically, it is essential to understand their biological function. Our group has contributed to the knowledge of glioma stem cells by developing an effective method to isolate them. This allows us to study their cellular characteristics as well as their contribution to the organization and architecture of the tumour tissue. This research project is divided into two complementary axes in line with our previous research.

A major feature of tumours is their ability to recruit new blood vessels to ensure a supply of oxygen and nutrients. This phenomenon, called angiogenesis, is associated with malignant progression of gliomas, but the interaction of stem cells with nerve tumour vessels and their dependence on angiogenesis is poorly understood. In our first research project, we study specifically this aspect of the biology of gliomas. We hope that our results will provide the knowledge necessary for a treatment strategy targeting tumour stem cells and glioma as well as provide new insight into angiogenesis.

As our group is specialized in the isolation and characterization of initiating cells, we hope to use the technology that we have developed to isolate and characterize initiating cells for other types of tumours. We will focus on the study of melanoma for the following reasons: First, metastatic melanoma is among the most aggressive cancers; the prognosis for this type of cancer remains extremely low. Second, during embryonic development, neural crest cells give rise to glial and melanoma cells. Due to this common ancestor, we hypothesize that the cells giving rise to glioma and melanoma may share physiological, phenotypic and molecular properties.

For these reasons, we propose, in the second project, to isolate the melanoma initiating cells from tumour tissue of human patients and to define the specific characteristics of these cells, as they may constitute a novel therapeutic target. The goal would be to develop a new approach in the treatment of metastatic melanoma based on technology developed in glioma.

Cohen Marie | **Novel therapeutic approaches against ovarian cancer recurrence**
Département de gynécologie et d'obstétrique, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2012 – 31.12.2014

Ovarian cancer affects 600 to 700 women each year in Switzerland. It is the leading cause of death among gynaecological cancers. Most ovarian cancers are diagnosed at an advanced stage of the disease, when the survival rate is very low. At an advanced stage, standard treatment is cytoreductive surgery followed by chemotherapy. Following this, most patients enter remission, but unfortunately most of them relapse. One strategy to reduce mortality from ovarian cancer would be to minimize relapse using targeted therapy after standard treatment.

The glucose-related protein 78 (GRP78) is a chaperone protein involved in the folding of proteins required for the survival of stressed cells such as cancer cells. GRP78 is suspected to induce tumour cell invasion and appears to play a critical role in certain cancer cells' resistance to chemotherapy. This protein is localized in the endoplasmic reticulum, but it is also observed on the surface of cancer cells and thus could be a "tumour-associated antigen". We have recently shown the presence of anti-GRP78 auto-antibodies in the serum of ovarian cancer patients. These antibodies promote apoptosis and decrease the invasiveness of cancer cells. Membrane localization of GRP78 specifically in cancer cells suggests that it may be a therapeutic target. That is why we propose to develop a targeted treatment combining photodynamic therapy, chemotherapy and immunotherapy to fight the recurrence of ovarian cancer. For this purpose, we will use vectors that are loaded with anti-cancer and/or photosensitizer agents and are covered with antibodies recognizing the same epitopes as the antibodies purified from serum of ovarian cancer patients. The drugs and/or photosensitizers will be encapsulated into the vectors.

Dietrich Pierre-Yves | **Identification and validation of glioma antigens: towards immunotherapies for brain tumours**
Service d'oncologie, Département de médecine interne, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2011 – 31.12.2013

For over 10 years, the goal of our research is to better understand how our immune system can defend us against the development of tumours in the brain and, on this basis, to develop new therapeutic strategies such as immunotherapies. Triggering an effective immune response and using lymphocytes as "killer cells" targeting tumour cells seems realistic, but it is essential that this response is selective, meaning that the lymphocytes kill specifically tumour cells, while leaving the normal cells of the brain untouched. Up to now, this selectivity seemed impossible in the absence of structures (called antigens) selectively expressed by tumour cells (and not expressed on normal cells). This is no longer the case. Indeed, thanks to collaboration with a spin-off of the University of Tübingen (Immatics), we have identified 10 interesting glioma antigens.

The goal of this project is to characterize these antigens to ensure that they are (1) overexpressed by tumour cells (almost no expression on normal cells should greatly reduce the risk of autoimmunity and toxicity), (2) immunogenic, meaning capable of eliciting an immune response, not only in healthy individuals but also in glioma patients, and (3) expressed in glioma stem cells, which play an essential role in the resistance of cancers to standard therapies (radiotherapy, chemotherapy). We hope to confirm that these glioma antigens are ideal targets for future immunotherapies in both vaccine and cellular therapy strategies.

Irminger Irmgard | **Regulation of the oncogenic isoforms of the tumour suppressor BARD1 in cancer by microRNAs and non-coding RNAs**
Département de gynécologie et d'obstétrique, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2012 – 31.12.2013

BARD1 is the constitutive partner of BRCA1, some mutations of which predispose to breast cancer. The ubiquitin ligase activity of BARD1-BRCA1 has a role in numerous onco-suppressor functions, especially within the cell cycle, in regulating the transcription and distribution of damaged DNA. The expression of different isoforms of BARD1, the outcome of alternative splicing, is incriminated in breast, colon, and lung cancers. Studying the mechanisms regulating BARD1 expression is therefore of key importance.

Our preliminary findings showed that the microRNA miR-203 regulates the expression of BARD1 in cancer cells. MicroRNAs are thought to be important regulators of carcinogenesis and may be used clinically as biomarkers and agents or as therapeutic targets. We have discovered a new non-coding isoform of BARD1 (9'L) expressed in cancer cells. Its expression is correlated to the expression of other BARD1 isoforms; it is significantly overexpressed in cancer tissues. We therefore hypothesize that RNA 9'L inhibits tumour-suppressor microRNAs and induces the expression of oncogenic isoforms of BARD1. This microRNA regulatory mechanism by "decoy" RNAs had been described only recently and appears to play a significant role in carcinogenesis.

In this project, we aim to evaluate in greater depth the role of miR-203 and other microRNAs in the regulation of BARD1. We will confirm the decoy RNA properties of 9'L and evaluate its functions in the regulation of BARD1 and microRNAs. We will also evaluate the diagnostic utility of 9'L and miR-203 for the clinical care of patients in a large cohort. Finally, we will extrapolate our research findings into a trial for clinical application. The research project described here is therefore not only of fundamental scientific value for future cancer biology but will also enable the uptake of its results for the promotion of innovative clinical methods.

Kruithof Egbert | **Epigenetic regulation of tissue factor and plasminogen activator in acute promyelocytic leukaemia cells**
Faculté de médecine, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2012 – 31.12.2012

Even quite recently, acute promyelocytic leukaemia had a high mortality rate. Under normal conditions, promyelocytes differentiate into mature cells. In promyelocytic leukaemia there is fusion between the PML gene and the retinoic acid receptor (RAR) gene. The resulting protein (PML-RAR) blocks the differentiation of promyelocyte under the effect of normal concentrations of retinoic acid (vitamin A). This leads to an expansion in the number of cells inhibiting the formation of other blood cells, resulting in clinical syndromes that may sometimes be fatal: anaemia, weakened immune defences and haemorrhage. Treatment with high doses of retinoic acid forces the promyelocytic leukaemic cells to differentiate and allows the blood count to re-establish itself.

A complication of leukaemia and treatment with retinoic acid is disseminated intravascular coagulation (DIC), the effect of which is to deplete blood coagulation factors. It may lead to haemorrhage, which is often fatal. Retinoic acid forms a complex with RAR that binds to DNA. This induces a modification in the DNA environment with positive effects, such as differentiation of leukaemic cells, and negative effects such as that described above on blood coagulation. Modifications in the DNA environment without modification in DNA sequencing belong to what are called "epigenetic modifications". We recently showed in other cell types that the production of various coagulation factors is modified by certain epigenetic modulators. A better understanding of the epigenetic mechanisms that regulate the expression of coagulation factors by promyelocytic leukaemic cells and the differentiation of these cells could improve the management of patients with leukaemia.

Mandriota Stefano | **Assessment of the carcinogenicity of aluminium chloride in human mammary gland epithelial cells**
Département de pédiatrie, Division d'onco-hématologie, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2011 – 31.12.2012

Aluminium salts, present in deodorants at high concentrations, have been suspected for some time to be carcinogenic to the breast, following the absorption and lymphatic drainage from the skin. However, up to now, no epidemiological or experimental data permitted conclusions. In our laboratory, using models of normal human mammary epithelial cells, we found that aluminium salts at concentrations up to 100,000 times lower than those found in deodorants induce morphological and functional changes typical of malignant transformation. This project proposes to study those changes in detail for their potential impact on the mechanisms of breast carcinogenesis.

Mandriota Stefano | **The ATM/p53 signalling pathway in the regulation of cellular senescence**
Département de pédiatrie, Division d'onco-hématologie, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01.01.2012 – 31.12.2014

The p53 tumour suppressor protein plays a key role in the induction of cellular senescence, which is an important barrier to cancer development. However, very little is known about the physiological mediators of cellular senescence induced by p53. CEACAM1 is an immunoglobulin superfamily member whose expression is frequently lost in human tumours and exhibits tumour suppressor features in several experimental systems including CEACAM1 knockout mice. There is currently little understanding of the pathways and mechanisms by which CEACAM1 exerts its tumour suppressor function.

We recently found that CEACAM1 is strongly upregulated during the cellular response to DNA double strand breaks (DSBs) and that upregulation is mediated by the ataxia telangiectasia mutated (ATM)/p53 pathway. Stable silencing of CEACAM1 showed that CEACAM1 is required for the induction of p53-mediated cellular senescence in response do DNA damage. These findings identify CEACAM1 as a key component of the ATM/p53-mediated cellular response to DNA damage, and as the first established tumour suppressor gene mediating cellular senescence downstream of p53. Our findings are detailed in a manuscript currently under revision for publication in *Cell Death and Differentiation*.

In this project, we propose to further elucidate the role of CEACAM1 in the induction of cellular senescence. In view of the novelty of the identification of CEACAM1 as a component of the ATM/p53 regulated DNA damage response and the well-defined features of CEACAM1 as a tumour suppressor, we strongly feel that the proposed project will provide important and fertile new insights into p53 and CEACAM1 tumour suppressor function and into the regulation of cellular senescence.

Reith Walter | **Identifying the cellular functions and regulatory networks that underlie the link between microRNA-155 and cancer**
Département de pathologie et d'immunologie, Faculté de médecine, Université de Genève, Genève
Duration: 01.01.2012 – 31.12.2014

MicroRNAs constitute a class of small, single-stranded, non-coding and well-preserved RNAs. By binding to target messenger RNAs, they cause them to be broken down or silence their ability to translate proteins. Post-transcriptional regulation by these microRNAs is involved in a great variety of essential physiological functions as well as in several diseases, in particular in the onset and development of cancer. MicroRNA-155 (miR-155) has been implicated in the development of cancer, but the target genes of this microRNA have yet to be identified.

The objective of this study is to attain a better understanding of the link between miR-155 and cancer by shedding light on its biological functions and its target genes in dendritic cells (DCs). Recently we studied the role of microRNAs in the differentiation, maturation and function of DCs. We showed that activation of miR-155 is a general and preserved characteristic in the maturation of DCs. Moreover, analysis of DCs in knockout mice for miR-155 revealed that induction of miR-155 is necessary for the maturation of DCs. Using functional approaches and genomic analyses, we demonstrated that the c-Fos transcription factor is a direct target of miR-155 and that its expression needs to be suppressed in order for DCs to mature.

In future experiments, we suggest studying in detail the expression, enzyme activity and regulation of a new potential target of miR-155, arginase 2. In view of the known role of arginase in tumour progression and development, we will investigate the consequences of deregulating its expression, in particular on T-cell activation and proliferation. These studies should enable us to gain a better understanding of the mechanisms controlled by miR-155 in tumour development.

Thore Stéphane | **Steroid receptor RNA activator: a new target for modulating the hormonal response in cancer cells**
Département de biologie moléculaire, Faculté des sciences, Université de Genève, Genève
Duration: 01.01.2011 – 31.12.2013

Specific cancers of some organs, such as those affecting the breast, pancreas or colon, share a common feature: their growth and dangerousness are closely dependent on the presence of a number of hormones. Studying the impact of these hormones on the physiology of the cell, whether healthy or cancerous, is therefore of prime importance. These studies will enable us to develop treatments that target biological mechanisms identified as being hormone-dependent and thus to be more effective at eliminating cancer cells. In the past decade, it has been shown that the regulation of transcription by hormone receptors is one of the fundamental hormone-linked mechanisms. In studies on the regulation of transcription by hormones, an RNA known as steroid receptor RNA activator (SRA RNA) has proved to have a modulator role, being able to amplify or inhibit the action of hormones on transcription. This RNA is the first of its kind to display an action of this type, which alone represents a new level for the hormone-based regulation of activation pathways.

Obtaining molecular models that describe the specific association of SRA RNA with various nuclear hormone receptors or partners involved in the cell response to hormones is essential for our understanding of its action. Moreover, these atomic models may be used to identify and/or develop molecules able to modify its action. Thanks to these research programmes, we will have greater means at our disposal for combating hormone-positive cancers. Newly identified molecules of this kind could be used alone or in combination, which would thereby limit the possibilities that the cancer cells might develop resistance capabilities, which is a recurrent problem in cancer treatment.

Tille Jean-Christophe | **Role of heparan sulfate in endometrioid carcinoma: tissue remodelling, angiogenesis and lymphangiogenesis**
Département de pathologie clinique, Faculté de médecine, Université de Genève, Genève
Duration: 01.01.2011 – 31.12.2013

Angiogenesis and lymphangiogenesis enable the formation of new blood and lymph vessels in the endometrium in a process that occurs physiologically during the ovarian cycle and pathologically in tumour growth. Heparan sulphate anti-coagulants bind and activate anti-thrombin such as heparin. They are present in the endothelial basement membrane and endow healthy endothelium with anti-thrombotic properties. The distribution and modulation of heparan sulphate anti-coagulants during tissue plasticity are not known. They appear to be reduced under the pathophysiological conditions that permit cellular

invasion of the tissues. We are investigating the function of heparan sulphate anti-coagulants in vascular and tissue plasticity during tumour invasion of the endometrium *in vivo* and *in vitro*. The data obtained in this study will enable evaluation of the therapeutic potential of heparan sulphate anti-coagulants as modulators of tissue invasion in endometrial cancer.

Zaïdi Habib | **Multitracer molecular imaging of tumour metabolism, cell proliferation and hypoxia: a pathway to personalized targeted therapy**
Département de radiologie, Faculté de médecine, Université de Genève, Genève
Duration: 01.01.2011–31.12.2012

Molecular imaging is a new discipline that visualizes the functioning of cells and molecular processes in the living being. The emergence of molecular imaging is the outcome, first, of the remarkable progress made in non-invasive imaging techniques. Enhancement of spatial resolution in positron emission tomography (PET) or single photon emission computed tomography (SPECT) today allows investigations to be undertaken in laboratory rodents, while the detection sensitivity of magnetic resonance and optical and acoustic imaging techniques allows exploration down to the molecular level. And second, molecular imaging is the outcome of the development of molecular tools: radiolabelling, tracers and optic, magnetic and acoustic probes all now profit from the power of molecular engineering.

What is promised by molecular imaging in the basic sciences is considerable: the ability finally to be able to study the living organism, to investigate cell migration, differentiation and ageing longitudinally, and the response to environmental factors. In experimental medicine, molecular imaging is absolutely essential in order to identify the molecular determinants of pathological processes *in situ,* to evaluate new molecular treatments such as gene therapy, and to accelerate the development of medications (production of active ingredients, efficacy of vectors), etc.

This project aims to develop the hardware and software tools that enable high-resolution multimodal imaging for cancer-based research. An innovative and original principle for tomography design, PET is proposed as a method for investigating the ENT sphere. The development of software tools enabling the fusion and analysis of images obtained by this means is also part of this project. This model will be validated prior to its clinical application.

Grisons Cancer League

von Moos Roger | **Patient management study: telephone follow-up regarding new symptoms during treatment with oral fluoropyrimidine**
Medizinische Onkologie und Hämatologie, Kantonsspital Graubünden, Chur
Duration: 01.09.2011–31.12.2012

With this project, the side effects of capecitabine will be recognized at an earlier point in time. Advice on measures to be undertaken to alleviate the side effects will be given early in the treatment. Patients will learn how to deal with side effects and know what they can do about them. As a result, discontinuations and treatment interruptions will be avoided. Patients feel cared for and supported during the treatment and are supported in their self-management.

Neuchâtel Cancer League

Registre neuchâtelois des tumeurs
The Neuchâtel Tumour Registry was started in 1972. It is managed by a technical and scientific committee. It is funded in part by the canton (fixed subvention of CHF 115,000 per year) and by the Neuchâtel Cancer League.

Thurgau Cancer League

Kodex-Stiftung
Kodex is a three-step substance abuse prevention programme for adolescents. It is carried out by the Kodex-Stiftung (Kodex foundation), which has no political or religious affiliations, and local Kodex associations or associations supported by Kodex. They are charitable non-confessional organisations.

Krebsregister Thurgau
We need information in order to provide effective evidence-based prevention, early detection, and treatment as well as care, palliative care, psycho-oncology and rehabilitation. The Thurgau cancer registry provides us with those data.

Ticino Cancer League (Fondazione ticinese per la ricerca sul cancro)

Bertoni Francesco | **The methylome of splenic marginal zone lymphoma: an integration of epigenetic, genetic and clinical data**
Laboratorio di oncologia sperimentale, Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Duration: 01.01.2011–31.12.2012

The project aims to clarify, at the molecular biology level, the characteristics of special types of spleen lymphoma, with the goal to be able to offer targeted treatments.

Frattini Milo | **Investigation of the role of NEU3 in colorectal carcinogenesis and in prediction of the efficacy of EGFR-targeted therapies**
Istituto cantonale di patologia, Locarno
Duration: 01.01.2011–31.12.2013

This project will conduct an analysis of a number of proteins interacting directly with EGFR, a cellular receptor targeted in specific treatments of colorectal and lung cancers. The aim is to identify patients that could benefit from those treatments.

Grassi Fabio | **Purinergic signalling in the pathophysiology of central nervous system infiltration in T-cell leukaemia**
Istituto di ricerca in biomedicina (IRB), Bellinzona
Duration: 01.01.2011–31.12.2013

The project aims to analyse the interaction of some activators and the NOTCH gene, which is important in the formation of certain types of leukaemia. Those results could easily lead to the development of new therapeutic techniques for this leukaemia, which typically occurs in children.

Thelen Markus | **Detailed study of the interactions and subcellular distribution of the tumourigenic chemokine receptor CXCR7/RDC1 in lymphocytes**
Istituto di ricerca in biomedicina (IRB), Bellinzona
Duration: 01.01.2011–31.12.2013

Chemokines are small proteins secreted by the cells. Some chemokines control cells of the immune system, especially white cells. Defects in chemokines could lead to an abnormal proliferation of the lymphatic system, and they therefore represent a possible cause of certain lymphomas.

Zurich Cancer League

Bernasconi Michele | **Role of proprotein convertases in paediatric sarcomas: useful theragnostic targets?**
Experimentelle Infektiologie und Krebsforschung, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich

The treatment of cancer in children has specific requirements, because excessive use of chemotherapy and especially radiotherapy can lead to significant long-term sequelae. Next to the development of entirely new therapeutic options, one of our objectives is to identify new therapeutic targets. We have identified a family of proteases (proteolytic enzymes) that play an important role in the growth of paediatric sarcomas. We will investigate the role of these proteases in paediatric sarcomas in order to use them as targets for new therapies. In this project, we hope to be able to develop new protocols for the treatment of paediatric sarcomas with fewer side effects.

Bornhauser Beat | **Large scale drug response profiling to identify new targets in refractory leukaemia**
Forschungsgruppe Leukämie /Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich

Treatment of relapse in children's leukaemia is a major challenge. Using a microscope-based analysis platform, we record systematically the response of leukaemia samples to a variety of new therapeutic substances and compare these profiles with genetic information in order to identify specific patterns. We hope to develop new therapies for the treatment of relapse patients.

Cancer Network Zurich | **Contribution to the 2012 symposium**
Universität Zürich, Zürich

The 2012 symposium of the Cancer Network Zurich was held in collaboration with the Zurich Cancer League following their annual general meeting on 24 May in the ballroom at Alterszentrum Hottingen. It was conducted as an evening lecture, open to the public, on "Vielversprechende Krebsforschungsprojekte im Kanton Zürich". Under the moderation of Prof. Miklos Pless, MD, three researchers presented their projects supported by the Zurich Cancer League. Prof. Adriano Fontana, MD, discussed the cause of fatigue in cancer. Prof. Holger Moch, MD, presented the problematic resulting from the fact that cancer is composed of various cells. Prof. Anne Müller, PhD, taking the example of cancer vaccines research and stomach cancer, showed how unexpected research results can lead to totally new insights. The speakers presented their projects in non-technical language, giving the audience an overview of the quality and originality of cancer research in Zurich and a sense of the commitment of researchers.

Dedes Konstantin | **Screening for novel synthetic lethal treatment approaches in endometrial cancer: a drug library based approach**
Klinik für Gynäkologie, Universitätsspital Zürich, Zürich

The goal of the project is to discover new targeted combination therapies for PARP inhibitors in endometrial cancer. By means of a drug-screening array, comprising hundreds of different inhibitors, we will examine the most promising combinations on endometrial cancer cell lines.

Raineteau Olivier | **E proteins as transcriptional targets in experimental gliomas**
Zentrum für Neurowissenschaften Zürich, Universität Zürich und ETH Zürich, Zürich

Brain tumours contain stem cells. These cells are resistant to conventional therapies such as chemotherapy and radiotherapy. They are therefore responsible for the recurrence of tumours after treatment. Our goal is to transfer our knowledge about neural stem cells to cancer stem cells in order to develop new therapeutic approaches based on the manipulation of (b)HLH transcription factors, the E proteins.

Renner Christoph | **Boosting of NY-ESO-1 specific re-directed T-cells**
Klinik und Poliklinik für Onkologie, Medizinbereich Innere Medizin-Onkologie, Universitätsspital Zürich, Zürich

Monoclonal antibodies can be used to reprogram T-cells and thus specifically direct them against tumour cells. The effectiveness of this new immunotherapeutic approach can be tested in "humanized mice", meaning mice with a human immune system.

Riediger Thomas | **Pharmacological inhibition of inflammatory nuclear factor κB signalling as a possible treatment approach against the cancer anorexia /cachexia syndrome**
Institut für Veterinärphysiologie, Vetsuisse-Fakultät, Universität Zürich, Zürich

Cancer-related inhibition of food intake (anorexia) and the associated body weight loss (cachexia) are serious clinical problems in patients with cancer and have a negative impact on treatment success. The signal molecule, nuclear factor kappa B (NF-κB) is probably involved in the development of anorexia, mediated by the brain. In animal studies, we will test whether pharmacological inhibition of NF-κB attenuates the anorexia/cachexia syndrome. Another goal is to identify the brain structures and nerve cells involved in the inhibition of food intake. This could contribute to the development of other treatment approaches.

Sartori Alessandro A. | **MicroRNA-mediated repression of CtIP implications for genomic instability and lymphomagenesis**
Institut für Molekulare Krebsforschung, Universität Zürich, Zürich

Mutations in DNA, the carrier of genetic information, can lead to cancer. Since we are constantly exposed to mutagenic substances, our cells are equipped with different DNA repair mechanisms. The protein CtIP plays an important role in the repair of DNA double-strand breaks, and insufficient amounts of CtIP in mice lead to the formation of tumours (lymphomas). In this project we aim to determine whether the protein levels of CtIP are controlled by mircroRNAs, and whether the deregulation of microRNAs leads to a lack of CtIP, which in turn could contribute to the development of cancer.

Schäfer Beat | **Transcriptional repression of PAX3/FOXO1 by fenretinide**
Abteilung Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich

Vitamin A derivatives are currently being intensively tested for possible application as new cancer drugs. However, there are different theories regarding their mechanism of action. In this project, we will investigate the impact of a treatment with fenretinide, one of the vitamin A derivatives, on childhood rhabdomyosarcoma at the molecular level. We hope to gain new insight by examining the transcriptional regulation of the fusion gene PAX3/FOXO1, which is important for this type of tumour.

Programme research: Supporting translational and clinical research

From 2002 to 2012, the Swiss Cancer Research foundation (formerly Oncosuisse) supported translational and clinical research in the framework of two special funding programmes: Collaborative Cancer Research Projects (CCRP) and International Clinical Cancer Research Groups (ICP). Research work in the last two ICP was completed in 2011. In their place, since 2009 funding has been given to clinical research institutions via performance agreements (see also the text on the supported research organizations on pages 14–17).

Collaborative Cancer Research Projects (CCRP)

With the CCRP, multidisciplinary research collaborations with a longer-term duration of five or more years were supported. The focus was on supporting translational research studies that shorten the way from the laboratory to the hospital bed, so that new findings from basic research find more rapid clinical application. As is typical of the complex CCRP, several subprojects were conducted at different institutes at the same time. The aim was for diverse specialists in research and medicine to pursue a common objective, exchange their ideas, expertise, and findings, and in this way to improve and accelerate the knowledge gain.

The funding of grants totalling 10.1 million francs was provided for CCRP, of which the last project was completed in 2012. Funding of CCRP, which were long-term in design and earmarked large funds, was discontinued in 2011 in favour of funding translational research projects in the funding area "independent research projects".

Kurt Bodenmüller, lic. phil. nat.
Communications manager of the Scientific Office, Swiss Cancer League and Swiss Cancer Research foundation, Bern

Collaborative Cancer Research Projects (CCRP)

Completed research project

Sommer Lukas et al. | CCRP OCS 01972-12-2006 | CHF 1,898,500.–
Abteilung Zell- und Entwicklungsbiologie, Anatomisches Institut, Universität Zürich, Zürich
Neural crest-derived cancer stem cells in melanoma: their role in initiation, progression and therapeutic response

Completed research project in brief

Sommer Lukas et al. | **Neural crest-derived cancer stem cells in melanoma: their role in initiation, progression and therapeutic response**

CCRP OCS 01972-12-2006
Duration: 01. 01. 2008 – 31. 12. 2012
CHF 1,898,500.–

Melanoma is a particularly aggressive cancer that is becoming more and more common in Switzerland. Until recently, it was thought that tumours are made up of many similar cells that all show malignant growth and thus contribute to tumour formation. According to a more recent hypothesis, however, a tumour can be made up of malignant cancer stem cells and other, less aggressive tumour cells. Normally, stem cells are responsible for the generation and regeneration of organs. Very similarly, cancer stem cells can divide and develop into other tumour cells and in this way form the tumour. There are many indications that traditional treatment strategies target this central cell population only insufficiently. Effective tumour treatment therefore must attack mainly cancer stem cells.

Melanoma cells arise by malignant transformation of melanocytes, the pigment cells in our skin. These cells originate in the neural crest during embryo development. For this reason, in this collaborative project we investigated whether in human tissue there are cells with the characteristics of these special stem cells. In accordance with the hypothesis that melanoma might develop from cancer stem cells, in biopsies from patients with melanoma we identified melanoma stem cells with features of neural crest stem cells. We then showed experimentally that mainly in metastases, melanoma cancer stem cells are present that are responsible for both tumour initiation and tumour maintenance.

In addition, an interesting finding was that in all tumour tissue that we examined, one gene was especially active, a gene that in normal cells controls the stem cell programme. This gene, called Sox10, is essential for the cell division and survival of stem cells. In studies with melanoma cells from tumour biopsies, we determined that this gene controls a stem cell programme also in cancer cells and is required for cell division. To confirm these findings in a living organism, we then used a mouse that carries a similar genetic mutation to that in human melanoma and that therefore spontaneously develops skin cancer. Astoundingly, suppression of Sox10 in this mouse model completely prevented the initiation and also the spread of cancer.

Our research shows that a tumour can probably be treated by attacking its stem cell programme. For this reason we are currently studying the factors that regulate, and are regulated by, Sox10. Knowledge about these stem cell regulators will be able to serve as a foundation for the development of new treatments. Indeed, we have already identified chemical components that prevent the division of tumour stem cells and, at least in the mouse model, work against the development of tumours. Our findings also show clearly that these investigations can lead to success mainly through close collaboration and deliberately utilized synergies among stem cell researchers, dermatologists, pathologists, and pharmacists.

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From personalized diagnosis to individualized treatment

Cancer diagnosis and treatment have changed greatly in recent decades due to numerous technological advances and a deeper understanding of tumour biology. For many centuries, tumour diagnosis was based on physical examination and personal and family medical histories, and treatment was largely restricted to symptom-oriented relieving of suffering. Surgical procedures were used only in few cases – mostly external tumours involving the skin. When medicine became a natural science-oriented discipline, the bases and concepts of cancer diagnosis and treatment also changed.

Aims of patient-centred cancer medicine

The success or failure of cancer treatment is decisively dependent on the characteristics of the tumour and characteristics of the patient. In addition to physical conditions of the patient such as age, previous illness, and co-medication, social, psychological, and environmental factors also influence treatment to varying conscious and unconscious degrees. But it is the characterization of the biological characteristics of the tumour that creates the necessary prerequisite for personalized (also called stratified or individualized) cancer medicine.

To do this, tumour cells are examined for certain biological characteristics – called biomarkers – at the level of the genes (DNA), primary gene products (RNA), and proteins. Depending on the biomarker, their identification may provide:

- prognostic information: assessment of the probable course of an illness, for example the risk of relapses and metastases
- predictive information: assessment of the findings allows the most promising treatment concept to be chosen
- and pharmacodynamics information on the effects and side-effects of drugs.

Prof. Holger Moch, MD
Director of the Institute of Surgical Pathology, Zurich University Hospital

Matthias Rössle, MD
Senior physician of the Institute of Surgical Pathology, Zurich University Hospital

Diagnostic examinations that take into consideration as far as possible all of these molecular changes of tumour cells form the basis of optimized treatment. New-generation substances that have the highest and most targeted effectiveness and at the same time minimized undesired side-effects play an important role here.

Foundations of morphological cancer diagnosis

Cellular pathology, which was decisively shaped by Robert Remak and Rudolf Virchow, assumed that the development of all diseases was at the cellular level ("omnis cellula e cellula"); this led to a radical change in cancer diagnosis. Since the second half of the nineteenth century, practically all potentially cancerous findings are examined morphologically at the level of tissue and/or cell. There is a certain irony in the fact that Virchow, as late as in 1860, wrote in an editorial that microscopes were not necessary in tumour diagnosis.[1] He was of the opinion that skin carcinomas do not develop from the surface epithelium but instead in connective tissue. (In fact carcinomas start in epithelial cells, the outermost cell layers of skin and mucosal tissue.)

Advances in microscope and staining techniques, especially the development of various histochemical and immunohistochemical staining methods, make more and more detailed pictures of tumours and their specific cellular and subcellular characteristics possible. In the past 20 to 30 years, new techniques have also been developed, including DNA cytometry, fluorescence *in situ* hybridization, and comparative genomic hybridization, which can detect changes in the chromosomes that have a role in cancer.

Development of modern cancer diagnosis

The decoding of the human genome more than 10 years ago and the development of new techniques make possible today ever faster and more extensive analysis of all genes (genome), gene products (transcriptome), proteins (proteome), and metabolic products and pathways (metabolome) of cells. The first of these tests to be used were PCR-based multigene expression assays (for example, EndoPredict and Oncotype DX) to assess risk in breast cancer. To determine the most appropriate treatment, previously mostly single gene mutations or chromosomal changes were examined. Examples are the presence of the KRAS gene in its normal variant as a prerequisite for antibody treatment with cetuximab of metastatic colorectal cancer, and overexpression of the HER2 gene for treatment of breast cancer with the monoclonal antibody trastuzumab.

Today – especially in tumour research and increasingly also in tumour diagnosis – new sequencing techniques ("next-generation sequencing") make it possible to decode the complete genome more and more quickly and less expensively. Frequently, only those gene segments that contain the information on the production of the proteins are sequenced. In these segments most of the known disease-causing mutations, which make up only about one per cent of the entire genetic information of an organism are found. Pilot studies have demonstrated the importance of implementing such techniques in everyday oncological practice.[2]

A great advantage of these techniques is that in a single examination the existing tumour material can be examined for numerous genetic changes. For example, material obtained from an adenocarcinoma in the bronchi of the lung can at the same time be analysed for mutations and translocations (rearrangements of whole segments of chromosomes). This not only allows us to find out what cancer-specific gene changes there are but also to find out how

heterogeneously they appear within the diverse cells of the tumour sample. Based on these analyses the decision can be made as to what surgery, radiation therapy, and chemotherapy treatment types can be used and in what sequence and combination they could be used optimally.

Opportunities and challenges

One of the greatest challenges when using modern molecular techniques like next-generation sequencing is that at present we have little experience in how medicine should deal with the information generated. Especially in cases where genetic errors are found in very few tumour cells (in the extreme case, in one tumour cell), the relevance of the diagnostic finding for progression and treatment of the tumour is not clear. Here there is a great need for research, mainly for prospective clinical studies.

In this connection, diverse questions need clarification: What conditions must a tumour sample fulfil to be considered representative? Are a few cells sufficient – for example cells that are taken from a tumour by endoscopic fine-needle aspiration – for determining prognostic, predictive, and pharmacodynamic biomarkers? Does examination of the heterogeneity of the primary tumour allow conclusions to be drawn as to the characteristics of newly discovered metastases, or do they have to be analysed again?

Although in principle cell and tissue material that has been routinely extracted and fixed can be used for these modern examinations, it has been found that depending on the amount of material and its handling, the results vary in quality.[3] The problem is that up to now there are no standardized and certified protocols for these procedures. At present no cross-institutional quality assurance such as interlaboratory tests for the latest sequencing methods has been established.

But the great potential of modern cancer diagnosis is evident. Thanks to sequencing of the entire tumour genome or all protein-encoding DNA segments, it will be possible in the future to identify in individual tumours not only the on-average two to eight driver mutations that are responsible for the malignant alterations of the cells but also to find other gene changes that are less relevant for the development of the cancer.[4] Up to now, these so-called passenger mutations have not been searched for, despite the fact that they can have considerable treatment consequences.

The increasing importance of pathology

For pathologists, these developments mean, for one, that in the future they must include clinicians more in pre-analysis aspects such as sample selection and preservation. For another, based on their morphological expertise, they must decide what amounts of sample tissue have sufficient tumour cell material for the further analyses. It is also centrally important that pathologists not only present the findings to the treating physicians but also – for example in interdisciplinary tumour boards – critically comment on and classify them. For pathology as a special discipline, this means that it must develop more into a clinically and treatment-relevant branch of medicine and take on a more active role than before in oncological research and care.

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Prof. Holger Moch, MD

Holger Moch studied medicine at Humboldt-Universität zu Berlin. From 1988 to 1990 he worked as a resident in pathology at the Charité University Hospital – Universitätsmedizin Berlin. The following three years Moch was a pathology resident at the University of Basel. In 1994 he was a research fellow at the University of California San Francisco and a visiting fellow at Harvard Medical School in Boston. In 2001 he became director of the Surgical Pathology Unit at Basel University Hospital and three years later chairman of the Institute of Surgical Pathology at Zurich University Hospital. In 2004 he was named full professor of pathology at the University of Zurich and has been director of the Institute of Surgical Pathology at Zurich University Hospital since then. He is a member of the Scientific Committee of the Swiss Cancer League and the Swiss Cancer Research foundation, as well as the Cancer Commission of the canton of Zurich.

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Matthias Rössle, MD

Matthias Rössle studied medicine at the University of Regensburg and Ludwig-Maximilian-University in Munich, Germany. He earned a Doctor of Medicine at Ludwig-Maximilian-University in 2001 and was a resident at the Institute of Pathology there from 2001 to 2003. In 2003 he came to Switzerland to work at the Institute of Pathology at Cantonal Hospital Lucerne and then at Cantonal Hospital St. Gallen. Rössle is board certified as a pathologist *(Facharzt)* and board certified in cytopathology *(FMH-Schwerpunkt)*; he earned the Proficiency Certificate in Head & Neck Sonography in 2012. Since 2010 he has been a senior physician at the Institute of Surgical Pathology at Zurich University Hospital, on Holger Moch's team.

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List of completed research projects in 2012

Ballmer-Hofer Kurt | OCS 02100-08-2007 | CHF 205,700.–
Labor für Biomolekulare Forschung, Paul Scherrer Institut (PSI), Villigen
Structural and functional analysis of ligand-mediated activation of VEGF receptor 2; identification and characterization of structural motifs for the development of new receptor inhibitory drugs for anti-vascular tumour therapy

Basler Konrad | KFS 02443-08-2009 | CHF 169,400.–
Institut für Molekulare Biologie, Universität Zürich, Zürich
Characterization of the role of histone binding by the Wnt signalling components Pygo2 in murine models of breast cancer and colon cancer

Becher Burkhard | KFS 02441-08-2009 | CHF 203,000.–
Institut für Experimentelle Immunologie, Departement Pathologie, Universität Zürich, Zürich
Cellular and molecular characterization of IL-12-mediated tumour suppression

Donda Alena | OCS 02248-08-2008 | CHF 138,300.–
Centre Ludwig de l'Université de Lausanne pour la recherche sur le cancer, Université de Lausanne, Epalinges
CD1d-anti-tumour antibody bifunctional molecules to redirect the innate and adaptive immune responses to the tumour site

Dotto Gian-Paolo | OCS 02361-02-2009 | CHF 314,350.–
Département de biochimie, Faculté de biologie et de médecine, Université de Lausanne, Epalinges
Tumour-suppressing function of calcineurin/NFAT in keratinocytes

Gönczy Pierre | KLS 02160-02-2008 | CHF 187,800.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Uncovering novel mechanisms regulating cell division timing using C. elegans

Hottiger Michael | KLS 02396-02-2009 | CHF 261,700.–
Institut für Veterinärbiochemie und Molekularbiologie, Universität Zürich, Zürich
Multiplex analysis of the ionizing radiation induced signalling network at the single cell level

Hynes Nancy | KFS 02528-02-2010 | CHF 183,100.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Reciprocal cross-talk between low-density lipoprotein receptor-related protein 1 and receptor tyrosine kinases: implications for modulating in vitro and in vivo properties of breast tumour cells

Imhof Beat A. | OCS 02260-08-2008 | CHF 307,100.–
Département de pathologie et immunologie, Faculté de médecine, Centre médical universitaire (CMU), Genève
Blocking tumour angiogenesis and invasion

Knuth Alexander | KLS 02740-02-2011 | CHF 53,200.–
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The mechanism underlying Coley's Fluid-mediated control of cancer

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Studies on the role of TRAIL as a tumour metastasis promoter

Nardelli Haefliger Denise | OCS 02304-08-2008 | CHF 360,400.–
Unité de recherche du service d'urologie, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Combination of vaccination and administration of topical immunostimulants as immunotherapeutic approaches against early uro-genital cancers

Radtke Freddy | KLS 02387-02-2009 | CHF 316,700.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
The role of Notch and TSLPR signalling during skin cancer

Thoma Nicolas | OCS 02365-02-2009 | CHF 186,300.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
The molecular basis of the defence against skin cancer: structural studies of the DDB1-DDB2-XPC/Rad23 UV-damage handover complex

Tschan Mario P. | KFS 02486-08-2009 | CHF 262,500.–
Experimentelle Pathologie, Institut für Pathologie, Universität Bern, Bern
The importance of autophagy in normal and leukaemic myelopoiesis

Presentation of completed research projects in 2012

Ballmer-Hofer Kurt | **Structural and functional analysis of ligand-mediated activation of VEGF receptor 2; identification and characterization of structural motifs for the development of new receptor inhibitory drugs for anti-vascular tumour therapy**
(OCS 02100-08-2007)

Vascular endothelial growth factors (VEGFs) activate three receptor tyrosine kinases, the VEGFRs, numbered 1, 2, and 3, which regulate angiogenic and lymphangiogenic signalling. VEGFR-2 is the most prominent receptor in angiogenic signalling by VEGF ligands. The extracellular part of VEGFRs consists of seven immunoglobulin-homology domains (Ig-domains). Earlier studies showed that domains 2 and 3 mediate ligand binding, and structural analysis of dimeric ligand/receptor complexes by electron microscopy and small angle solution scattering revealed additional homotypic contacts in membrane-proximal Ig-domains D4 and D7. Here we showed that D4 and D7 are indispensable for receptor signalling.

To confirm the essential role of these domains in signalling, we isolated VEGFR-2 inhibitory antibody-like molecules binding the extracellular receptor domain. Some of these molecules inhibited ligand binding, receptor dimerization, and receptor kinase activation, whereas others did not prevent ligand binding or receptor dimerization but efficiently blocked receptor signalling and functional output. These data show that specific subdomains regulate VEGFR-2 activity. We propose that these extracellular domain-specific inhibitors represent a novel generation of receptor inhibitory drugs for *in vivo* applications such as targeting of VEGFRs in medical diagnostics and for treating vascular pathologies.

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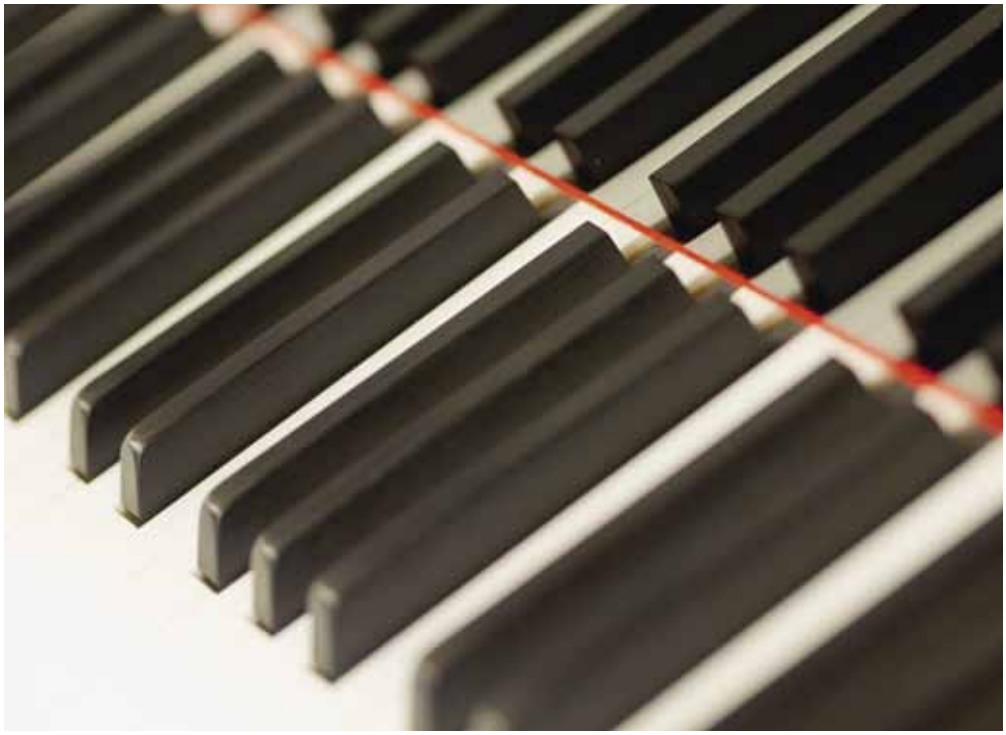
Basler Konrad | **Characterization of the role of histone binding by the Wnt signalling component Pygo2 in murine models of breast cancer and colon cancer**
(KFS 02443-08-2009)

The Wnt signalling pathway is one of a few biological pathways that control cell fate within complex organisms: it leads to the activation of a genetic programme that is crucial for the control of cell proliferation. When misregulated, Wnt signalling can directly cause cancers in humans: in particular, clinical evidence suggests a strong connection between the Wnt signalling pathway and two of the most aggressive human tumours, colon carcinoma and breast cancer. We focused our attention on one important Wnt pathway component, the protein Pygopus.

In humans and other mammals, Pygopus is located within the cell nucleus, where it acts as one of the final effectors of the signalling output, directly orchestrating Wnt-target gene regulation. Pygopus may do so in two ways: (1) it recruits multi-protein complexes to control the gene expression and thereby initiates the Wnt signalling specific programme, and (2) it acts as a decoding machine, reading the modifications present on histones. Histones are proteins that together with DNA constitute the chromatin. It has become clear that decoding the information found on histones is essential in determining which genes need to be activated and which repressed. Pygopus has this ability, and several recent studies suggested that its ability to interact with chromatin is involved in breast cancer formation.

In our project we set out to clarify the relevance of Pygopus as a potential player in the regulation of Wnt target genes that are relevant for human cancers. Our strategy comprises the use of the mouse as a model organism: we generated a genetically modified mouse strain in which the endogenous Pygopus had been substituted with a Pygopus variant that is unable to bind histones. We assessed the specific contribution of this function of Pygopus during mouse embryonic development and, in adult mice, during cancer formation and progression. Our research surprisingly revealed that when the selected interaction is abolished, this does not lead to any major defect



during embryonic development in mice. However, we envision the possibility that, whereas not disturbing normal homeostatic processes, perturbing the function of Pygopus might lead to subtle defects in the expression of certain Wnt target genes that are relevant for cancer formation and progression. Additional studies are required to study the specific contribution of Pygopus in cancer formation and metastasis progression in humans.

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Becher Burkhard | **Cellular and molecular characterization of IL-12-mediated tumour suppression**
(KFS 02441-08-2009)

Immune cells communicate with each other through the use of a specific type of proteins called cytokines. Cytokines are produced by immune cells and target other immune cells equipped with a receptor sensing the specific cytokine. Interleukin 12 (IL-12) is such a cytokine and has been demonstrated to have powerful anti-tumour effects. But as to how exactly IL-12 blocks tumour growth remains a matter of debate. Whereas IL-12 has been demonstrated to bind to a variety of different immune cell types, we identified a new population of innate lymphocytes (ILCs) to sense IL-12 and to alter tumour blood vessels. In addition, we found that IL-12 acts directly within the tumour and does not need to be supplied systemically to have therapeutic effects. Whereas immunomodulatory therapies are often rendered void within the tumour tissue, manipulating tumours directly with IL-12 can aid the optimal development of a protective anti-tumour immune response.

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Donda Alena | **CD1d-anti-tumour antibody bifunctional molecules to redirect the innate and adaptive immune responses to the tumour site**
(OCS 02248-08-2008)

Upon their activation by the MHC I-like protein CD1d expressed on antigen-presenting cells, the subpopulation of iNKT lymphocytes is able to stimulate the innate (NK cells, dendritic cells) and adaptive (CD4 and CD8 T- and B-lymphocytes) immune responses, and their resulting anti-tumour effects are well demonstrated. During the initial phase of this project, we showed that the genetic fusion of the CD1d molecule with an anti-tumour antibody fragment against HER2 or CEA resulted in the growth inhibition of tumours overexpressing these tumour antigens. The anti-tumour effects obtained in mouse tumour models were associated with the infiltration of the tumour tissue by iNKT, NK, and T-lymphocytes, which are all able to kill tumour cells.

More recently, we confirmed the specific targeting of CD1d-anti-tumour fusion proteins on human tumour cells when expressing the antigens HER2 or CEA, leading to their destruction by iNKT cells isolated from healthy donors. The CD1d-anti-tumour proteins are efficient in inducing the proliferation and cytokine release of human iNKT cells, and most importantly, they lead to direct tumour cytotoxicity, in contrast to the dendritic cell-mediated iNKT cell activation. In that case, the dendritic cells themselves become targets and are preferentially killed by iNKT cells instead of the tumour cells. The genetic fusion of CD1d to additional anti-tumour antibody fragments will allow the targeting of iNKT cells to various types of tumours. More and more, anti-cancer treatments are combining different approaches in order to attack the tumours on different fronts and avoid tumour escape. In this context, the immunoregulatory properties of iNKT cells offer various combinations to promote the innate and adaptive anti-tumour immune response at the tumour site.

In particular, our recent results combining CD1d-anti-tumour immunotherapy with a therapeutic cancer vaccine resulted in a synergistic tumour inhibition associated with the accumulation of not only NK cells but also tumour-specific T-lymphocytes. The powerful growth inhibition of established tumours suggests that this combined immunotherapy will allow the creating of long-term immunity against the cancer cells, able to prevent tumour relapse after surgery.

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Dotto Gian-Paolo | **Tumour-suppressing function of calcineurin/NFAT in keratinocytes**
(OCS 02361-02-2009)

Squamous cell carcinoma (SCC) of the skin is a major complication and cause of death for the many recipients of organ transplants treated with calcineurin-inhibitory drugs like cyclosporin A (CsA) to suppress organ rejection by the immune system. The tumour-promoting effects of calcineurin inhibitory drugs have been generally attributed to inhibition of the immune system and, in particular, T-cell function. However, whereas the risk of cutaneous SCC in CsA-treated patients is 65 to 100-fold higher than in the normal population, the incidence of other skin tumours, like basal cell carcinoma (BCC) or melanoma, or that of internal malignancies increases to a significantly lesser extent.

In a first set of studies, we found that mice with keratinocyte-specific genetic loss of calcineurin activity have increased susceptibility to chemically-induced skin carcinogenesis, with higher incidence of tumours and malignant conversion. In a second set of studies with human cells freshly derived from the skin of patients, we found that genetic and pharmacological suppression of calcineurin activity enhanced substantially the susceptibility of these cells to tumourigenic conversion and gave rise to SCC when retransplanted into mice.

In further studies aimed at exploring the underlying mechanisms, we found that calcineurin signalling inhibits expression of a transcription factor, ATF3, which functions as a negative regulator of a key tumour suppressor gene, p53. We consequently showed that in cells and patients treated with calcineurin inhibitors, expression levels of ATF3 are substantially increased, whereas those of p53 are downmodulated. Under these conditions, there is an expansion of cancer progenitor cells that are responsible for aggressive tumour formation.

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Gönczy Pierre | **Uncovering novel mechanisms regulating cell division timing using *C. elegans***
(KLS 02160-02-2008)

Mitosis represents a critical moment in the cell cycle that ensures notably that chromosomes are distributed in a faithful manner to daughter cells. Cancerous cells frequently have defects in the mechanisms regulating mitosis. For instance, the protein kinases polo-like kinase 1 (PLK1) and Aurora-A, which normally contribute to the onset of mitosis, are overexpressed in many tumours. Promising drugs that interfere with the activity of PLK1 or Aurora-A have entered the initial phases of clinical trials.

However, the therapeutic potential offered by such drugs is limited by the incomplete understanding of the underlying mechanisms. Our research was aimed at improving this understanding by using the assets of a model organism particularly well suited to address this question: the nematode *Caenorhabditis elegans (C. elegans)*.

We utilized an array of cell biological, molecular, and genomic approaches to dissect in this organism the mechanisms dictating the onset of mitosis, with a particular emphasis on the homologues of PLK1 and Aurora-A (called PLK-1 and AIR-1). We demonstrated that PLK-1 plays a critical role in modulating the timing at which the two daughter cells divide in the early embryo of *C. elegans*. Further, we executed a functional genomic screen aimed at identifying new proteins that contribute to AIR-1 function. These studies should contribute towards a better understanding of the mechanisms regulating cell proliferation, including in human tissues. In this manner, our research should eventually lead to the discovery of novel therapeutic agents for the benefit of the patient.

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Hottiger Michael | **Multiplex analysis of the ionizing radiation-induced signalling network at the single cell level** (KLS 02396-02-2009)

Study outline
Every cell is exposed to genotoxic stresses such as radiation or chemicals that can cause harmful and deleterious mutations in the genome. As protection, cells have evolved an intricate regulatory network to detect and repair DNA damage. Genotoxic stress signalling helps maintain genomic stability and thus prevents tumourigenesis. Up to now, technical and practical limitations prohibited a comprehensive deciphering of this regulatory network. In this project, we employed a new technology to assess the status of all major cellular signalling pathways after the exposure of primary human fibroblasts to ionizing radiation (IR). The results delivered new insights into molecular mechanisms and reveal how these cells are able to cope with high doses of IR.

Goals
It was the goal of this study to identify all cellular signalling pathways that enable primary human fibroblasts to withstand high doses of IR.

Methods
We generated and employed reverse protein arrays to simultaneously quantify hundreds of proteins involved in genotoxic stress signalling. Human cells were exposed to IR, and the changes in the proteome were quantified with specific antibodies for all key signalling components in the cell.

Results
This analysis provided new insights into the radiation-induced cellular signalling pathways and identified the activation of DNA damage response pathways as well as of pro-survival and anti-apoptotic markers. Proteins of the PKC family were activated early upon irradiation, suggesting a regulatory function in the IR response of primary human fibroblasts. Inhibition or downregulation of PKC in primary human fibroblasts caused IR-dependent downregulation of the identified pro-survival and anti-apoptotic markers and thus led to a proliferation stop and to apoptosis. Our analysis suggests that cytoplasmic PKC signalling conditions IR-stressed primary human fibroblasts to prevent irradiation-induced apoptosis.

Relevance for cancer research
These findings contribute to the understanding of the cellular and nuclear IR response and may thus eventually improve the efficacy of radiotherapy and help overcome tumour radioresistance.

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Hynes Nancy | **Reciprocal cross-talk between low-density lipoprotein receptor-related protein 1 and receptor tyrosine kinases: implications for modulating *in vitro* and *in vivo* properties of breast tumour cells** (KFS 02528-02-2010)

Breast carcinoma is the most frequent cancer in women. Despite the often successful surgical removal of primary breast tumours, many patients die from metastases. Metastasis is a complex process whereby tumour cells acquire invasive properties and colonize distant sites. PN-1, an extracellular serine protease inhibitor, is highly secreted by some tumour cells and is internalized into cells via the LRP1 receptor. PN-1 levels are significantly elevated in certain aggressive breast cancer subgroups. In a project previously funded by the Swiss Cancer League, we showed that PN-1 binding to LRP1 activates intracellular signalling, leading to the production of matrix metalloproteinase-9 (MMP9), a known player in tumour invasiveness. Upon reduction of PN-1 in the tumour cells, MMP9 levels are decreased and have a significantly decreased metastatic ability. Re-expression of MMP9 rescues their metastatic potential. This suggested that the prevention of PN-1 binding to its receptor would negatively affect tumour metastasis and could be a novel target for metastasis prevention.

To test this hypothesis, we produced a PN-1 blocking antibody (Ab), which our results show has a strong impact in combination with a FGFR inhibitor on the metastatic spread of an aggressive breast cancer model *in vivo*. Using intravital multiphoton imaging, we showed that the microenvironment in mammary tumours from the PN-1 Ab treated mice is altered when compared to that of control tumours. The most striking effects were on the density of the extracellular collagen matrix in these tumours, which could contribute to the measured decreased level of circulating tumour cells and decreased lung metastases in the treated animals. These effects were even more striking in mice treated with a combination of PN-1 Ab and FGFR inhibitor.

Cross-talk between tumour cells and different host cells influences malignancy. We are investigating whether this cross-talk is altered by blocking PN-1 from activating the LRP-1 receptor in the tumour microenvironment. We will further delineate the role of MMP9 in altering the microenvironment downstream of PN-1/LRP1 and FGFR and examine whether other signalling pathways play a role in this process. PN-1 plays multiple roles in modulating the metastatic tumour microenvironment, and our *in vivo* data suggest that it may be therapeutically beneficial to target PN-1 in combination with FGFR and that our approach may be generally applicable in mitigating cancer metastasis.

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Imhof Beat A. | **Blocking tumour angiogenesis and invasion** (OCS 02260-08-2008)

Tumour growth depends on nutrients and oxygen, transported into the tumour by newly formed blood vessels. This process is called angiogenesis and is mediated by the growth factor VEGF. Our main objective was to find new targets involved in the process of angiogenesis. Initially, we focused on the endothelial adhesion molecule JAM-C, which was already described by us as a potent target for combined anti-tumour therapy. In the past years, we continued to focus on JAM-B, the counter-receptor of JAM-C, and on NOX1, a molecule implicated in endothelial cell physiology and oxidative stress. We identified JAM-B and NOX 1 in endothelial cells as molecules regulating the main angiogenesis growth factor VEGF by using a combination of pharmacological and genetic methods.

We found that anti-JAM-B and anti-VEGF receptor antibodies act in synergy to block tumour growth. Further, we found that the blocking of NOX 1 also resulted in decreased tumour angiogenesis and tumour growth. These effects were due to reduced production of VEGF, as it affects the gene regulatory protein PPARα, which controls VEGF production. These results provide novel ways for to develop anti-tumour therapies by blocking tumour angiogenesis.

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Knuth Alexander | **The mechanism underlying Coley's Fluid-mediated control of cancer** (KLS 02740-02-2011)

Study design
The immune system is able to recognize and eliminate cancer cells. Recently, it was shown that the microenvironment of tumours actively inhibits the immune recognition of cancer. Knowing this, reactivating the immune system against cancer (immunotherapy) can be a treatment option. William Coley (1862–1936) was one of the first to use an immunotherapeutic approach to cancer without understanding the pathophysiology. Coley observed that patients eliminated their cancer after a severe infection, and he began to investigate this clinical observation systematically. He found that some patients injected with a mixture of dead bacteria (called Coley's fluid, Coley's vaccine, or Coley's toxins) indeed showed tumour regressions. Today, we think that Coley's toxins activate the innate immune response, which is crucial for the development of protective, specific immunity. For cancer patients this would imply that treatment with Coley's toxins may stimulate tumour-specific immunity and thus result in tumour control.

Methods
We investigated the effects of Coley's toxins on innate and adaptive immune responses in mice. Further, we established protocols to treat melanoma in a mouse model.

Results
We found that injection of Coley's toxins induces a massive inflammatory response, resulting in lymphocyte activation, dendritic cell maturation, inflammasome activation, and production of pro-inflammatory cytokines. Repeated treatment with Coley's toxins supported tumour-specific immunity and resulted in control of experimental melanoma. We are currently investigating whether additional treatments that result in immune stimulation further improve the efficacy of Coley's toxins.

Relevance
Our project has a scientific and a translational aspect: the first aims to improve our current understanding of the interaction between the immune system and cancer, a nd the second aims to investigate whether the controlled use of Coley's toxins can become a therapeutic modality for cancer patients.

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Martinou Jean-Claude | **Studies on the role of TRAIL as a tumour metastasis promoter**
(KLS 02370-02-2009)

TRAIL is a ligand of the tumour necrosis factor (TNF) family that binds to a specific receptor at the surface of most cell types. Upon binding to its receptor, TRAIL stimulates apoptosis of cancer cells but leaves healthy cells intact. HCT116 colon cancer cells are particularly sensitive to TRAIL: upon incubation with TRAIL, cultured HCT116 cells rapidly detach from the plate and undergo apoptosis. In contrast, HCT116 cells lacking Bax, a pro-apoptotic member of the Bcl-2 family playing a key role in the intrinsic pathway of apoptosis, resist TRAIL. Importantly, we observed that upon TRAIL treatment, Bax-deficient HCT116 cells also detached from the plate, migrated, then reattached and proliferated. This propensity of Bax-deficient cells to detach and to migrate in the presence of TRAIL was due to the activation of the ROCK kinase. We also observed that the combination of TRAIL and a proteasome inhibitor promoted apoptosis, also in cells lacking Bax and displaying a defective intrinsic pathway of apoptosis.

In summary, our results suggest that a TRAIL therapy of cancer cells with a defective intrinsic pathway of apoptosis may be deleterious, as this could promote metastasis. In contrast, a combined therapy of TRAIL and proteasome inhibitors may be useful to promote apoptosis of cells lacking a functional intrinsic apoptotic pathway.

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Nardelli Haefliger Denise | **Combination of vaccination and administration of topical immunostimulants as immunotherapeutic approaches against early uro-genital cancers** (OCS 02304-08-2008)

Background
Vaccination for inducing anti-tumour responses is a promising strategy to fight cancer, although with only limited clinical outcomes to date. In the case of tumours located in mucosa, such as cervical cancer and bladder cancer, adapted strategies are necessary to address efficient immune responses to the tumour sites.

Study objectives
In this project, we tested a novel immunotherapeutic method that combines tumour antigens vaccination with the administration of immunostimulants directly on the tumour sites in the genital or bladder mucosa.

Methods
Murine pre-clinical models for cervical cancer and bladder cancer have been established. Vaccinated mice are intravaginally or intravesically (depending on tumour location) administered with immunostimulants (synthetic molecules or bacteria). Then, either the presence of anti-tumour immune cells (killer T-cells) in the mucosa or the effects of the combined treatment on tumour regression are analysed.

Results
Our data showed that local immunostimulation led to an increase in the number of anti-tumour killer T-cells in the genital or bladder mucosa. More interestingly, this combined treatment was able to induce efficient regression of established genital tumours that were resistant to vaccination alone.

Potential patient benefit
This novel strategy is promising for treating uro-genital cancers. It will be worth testing whether the anti-tumour responses induced by a cancer vaccine could be improved by the intravesical instillation of bacteria (BCG), which is the standard treatment for patients with non-muscle invasive bladder cancers at risk of progression.

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Radtke Freddy | **The role of Notch and TSLP signalling during skin cancer** (KLS 02387-02-2009)

Background
Notch receptors mediate cell-to-cell communication and regulate thereby diverse effects of cell behaviour including growth, migration, and differentiation. The skin expresses multiple Notch receptors (Notch1–3). Using mouse genetics, we previously showed that skin-specific long-term inactivation of Notch1 results in skin cancer. Simultaneous loss of Notch1 and Notch2 did not result as predicted in a faster onset of skin cancer but instead resulted in a severe form of atopic dermatitis also known as eczema. The atopic dermatitis is due to excessive production of the cytokine thymic stromal lymphopoietin (TSLP) by Notch-deficient keratinocytes.

Goal of study
Inflammation can influence cancer growth. Dependent on the type of inflammation it can promote or inhibit tumour progression. The goal of this study was to investigate if and how TSLP-mediated inflammation promotes or fights skin cancer.

Methods
We used and combined different genetically engineered mouse models in which Notch receptors can specifically be inactivated in the skin. These mice were used as hosts for adaptive bone marrow transplantations, with the goal to reconstitute their blood system with cells that can no longer respond to the cytokine TSLP. Using this method we investigated whether the skin-specific inflammation changes are due to the unresponsiveness to TSLP and whether this may influence the development of skin cancer.

Results
Our experiments showed that TSLP-mediated inflammation activates T-cells of the immune system in the skin and thereby fights cancer. As a consequence of inhibiting TSLP-mediated inflammation, T-cells are no longer present in the area where skin tumours develop. Moreover, the cellular composition of the inflammation changes, resulting in a pro-tumourigenic type of inflammation.

Relevance
Our studies showed for the first time, that TSLP-mediated inflammation could protect against skin cancer by its ability to activate T-cells of the immune system. Thus, eczema is not necessarily a bad thing. Artificial induction of eczema might therefore be beneficial in the context of skin cancer.

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Thoma Nicolas | **The molecular basis of the defence against skin cancer: structural studies of the DDB1-DDB2-XPC/Rad23 UV-damage handover complex**
(OCS 02365-02-2009)

Genetic instability is a hallmark of all cancer cells. The loss of genetic information functions as an initiator in the formation of the tumour cells as well as in driving the malignant transformation process. Persistent UV irradiation of exposed skin cells leads to an accumulation of DNA lesions. If left unrepaired, these DNA damages facilitate formation of skin tumours ranging from malignant melanomas and squamous cell carcinomas to basal cell carcinomas.

This study focussed on the DDB1-DDB2 protein complex and its interactions with the XPC/Rad23 complex. Together these complexes recognize DNA damages and initiate the repair response. We aimed to use a combination of the X-ray crystallography and biochemical techniques to understand how these crucial protein complexes detect and repair DNA damage, and thus serve as a safeguard against skin cancer. We determined the structure of the DDB1-DDB2-Cul4 complexes and determined on the molecular level how damage binding activates the complex.

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Tschan Mario P. | **The importance of autophagy in normal and leukaemic myelopoiesis**
(KFS 02486-08-2009)

Study design
Autophagy, which literally means "self-eating", is a degradation mechanism mainly involved in the recycling and turnover of cytoplasmic constituents, including cell organelles and aggregated proteins. Autophagy is characterized by the formation of particular organelles, the autophagosomes. Autophagy allows healthy cells to maintain homeostasis and to survive "stressful" conditions such as nutrient deprivation. Defects in the autophagy pathway may lead to neurodegenerative and heart diseases as well as to cancer. Basal autophagy has tumour-suppressive functions by degrading defective organelles or mutant proteins. Conversely, autophagy may allow survival of cancer cells upon cancer therapy. The function of autophagy in the pathogenesis of acute myeloid leukaemias (AML), a disease characterized by the accumulation of immature white blood cells, has only been scarcely studied.

Aim
To decipher the role of autophagy in AML pathogenesis.

Methods
Currently, oral retinoic acid treatment is used in an AML subgroup to induce neutrophil differentiation of the leukaemic blast cells. We inhibited autophagy during this process using pharmacological and genetic inhibitors of autophagy. Moreover, we determined the autophagy gene expression profile in clinical AML patient samples.

Results
We found that blocking autophagy impaired retinoic acid-induced differentiation of AML cells. Interestingly, we identified a novel type of autophagy – myeloid differentiation-associated autophagy – that is clearly different from starvation-induced autophagy. Further, combining retinoic acid with drugs activating autophagy resulted in significantly improved neutrophil differentiation of AML cells. In general, we found that the expression of most autophagy genes is attenuated in primary AML.

Potential benefit for patients
In summary, we suggest that activating autophagy with currently available drugs will improve differentiation therapy in AML. Particular cancer therapies use drugs with a negative effect on autophagy, and it has to be taken into consideration that there could be adverse effects on neutrophil differentiation.

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Basic biomedical research

List of approved research projects in 2012

Total funds allocated: CHF 7,190,300.–

Aguet Michel | KFS 03022-08-2012 | CHF 255,300.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Role of BCL9 proteins in regulating WNT-mediated stem cell maintenance in WNT-activated human colorectal cancer

Ballmer-Hofer Kurt | KFS 02895-02-2012 | CHF 203,400.–
Labor für Biomolekulare Forschung, Paul Scherrer Institut (PSI), Villigen
Role of VEGF/VEGF receptor signalling in primary and metastatic tumour growth and pre-clinical evaluation of novel allosteric VEGFR-2 inhibitors

Becher Burkhard | KFS 02981-08-2012 | CHF 234,900.–
Institut für Experimentelle Immunologie, Departement Pathologie, Universität Zürich, Zürich
Using IL-12 in combination immunotherapy against late-stage glioblastoma

Bentires-Alj Mohamed | KFS 03029-08-2012 | CHF 183,100.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Oncogenic signalling networks downstream of PIK3CA mutations in breast cancer

Bodenmiller Bernd | KFS 03034-08-2012 | CHF 363,400.–
Institut für Molekulare Biologie, Universität Zürich, Zürich
Single-cell signatures and signalling states during the epithelial-mesenchymal transition and their relevance for breast cancer metastasis

Bourquin Carole | KFS 02910-02-2012 | CHF 109,700.–
Département de médecine, Université de Fribourg, Fribourg
Enhancing anti-cancer immunity through sequential stimulation of innate immune pathways

Chiquet-Ehrismann Ruth | KFS 02980-08-2012 | CHF 183,100.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Discovery of novel genes and pathways important for cancer progression and metastasis

De Palma Michele | KFS 03007-08-2012 | CHF 222,700.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Anti-angiogenic therapy for breast cancer: role of macrophages and microRNAs as effectors and biomarkers of tumour responses

Gasser Susan M. | KFS 03062-08-2012 | CHF 305,100.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
New approaches for targeting the S-phase checkpoint kinase ATR

Hanahan Douglas | KFS 03031-08-2012 | CHF 265,300.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Elucidating the role of tumour microenvironment in adaptive/evasive resistance and regrowth of residual disease after B-Raf driver oncogene inhibition in a mouse model of melanoma, and assessing the potential of angiogenesis and c-Met inhibitors to restrain such relapse

Hynes Nancy | KFS 03000-08-2012 | CHF 191,200.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Reciprocal cross-talk between low-density lipoprotein receptor-related protein 1 and receptor tyrosine kinases: implications for modulating in vitro and in vivo properties of breast cancer cells

Imhof Beat A. | KFS 02914-02-2012 | CHF 237,900.–
Département de pathologie et d'immunologie, Faculté de médecine, Université de Genève, Genève
Novel molecules for tumour treatment: angiogenesis, lymphangiogenesis, pericytes and immune cells

Katanaev Vladimir | KFS 02978-08-2012 | CHF 207,100.–
Département de pharmacologie et de toxicologie, Université de Lausanne, Lausanne
Antagonists of FZD7 as anti-triple negative breast cancer agents

Kaufmann Thomas | KFS 03014-08-2012 | CHF 203,800.–
Institut für Pharmakologie, Universität Bern, Bern
Investigating the role of the Bcl-2 family member BOK in tumourigenesis

Locher Kaspar | KFS 03004-08-2012 | CHF 226,000.–
Institut für Molekularbiologie und Biophysik, ETH Zürich, Zürich
Structural basis of inhibition of multidrug transporter ABCB1 by monoclonal antibodies

Lopes Massimo | KFS 03028-08-2012 | CHF 198,900.–
Institut für Molekulare Krebsforschung, Universität Zürich, Zürich
Mechanistic insight into oncogene-induced DNA replication stress

Ludewig Burkhard | KLS 02880-02-2012 | CHF 186,400.–
Institut für Immunbiologie, Kantonsspital St. Gallen, St. Gallen
Systems biology approach to molecularly characterize the lung cancer microenvironment

Meylan Etienne | KLS 02885-02-2012 | CHF 339,200.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Role of the antiviral innate response in the development of non-small cell lung cancer

Moreno Eduardo | KFS 03015-08-2012 | CHF 232,100.–
Institut für Zellbiologie, Universität Bern, Bern
FLOWER^{Lose}-activated p53 and FLOWER^{Ubi}-activated NF-κB determine the fate of cell-competition in solid tumours

Ochsenbein Adrian F. | KFS 02879-02-2012 | CHF 355,200.–
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
TRAF-binding TNF receptor signalling in leukaemia stem cells

Peter Matthias | KLS 02906-02-2012 | CHF 243,100.–
Institut für Biochemie, ETH Zürich, Zürich
Characterization of the human MMS22L-TONSL complex in maintenance of genome stability and prevention of carcinogenesis

Reith Walter | KFS 02888-02-2012 | CHF 179,700.–
Département de pathologie et d'immunologie, Faculté de médecine, Université de Genève, Genève
Identifying the cellular functions and regulatory networks that underlie the link between microRNA-155 and cancer

Ruiz i Altaba Ariel | KLS 02912-02-2012 | CHF 140,900.–
Département de génétique médicale et de développement, Faculté de médecine, Université de Genève, Genève
Small molecule inhibition of WNT-TCF signalling in colon cancer

Sartori Alessandro A. | KFS 03025-08-2012 | CHF 160,100.–
Institut für Molekulare Krebsforschung, Universität Zürich, Zürich
Identification of synthetic genetic interactions with the CtIP tumour susceptibility gene through functional RNAi screening

Schwaller Jürg | KFS 03019-08-2012 | CHF 227,400.–
Forschungsgruppe Kinderleukämie, Departement Biomedizin, Universitätsspital Basel, Basel
Modelling and targeting of aggressive human acute leukaemia driven by epigenetic regulators

Skoda Radek C. | KLS 02950-02-2012 | CHF 344,500.–
Forschungsgruppe Experimentelle Hämatologie, Departement Biomedizin, Universitätsspital Basel, Basel
The pathogenesis of myeloproliferative disorders

Sommer Lukas | KFS 02897-02-2012 | CHF 234,300.–
Abteilung Zell- und Entwicklungsbiologie, Anatomisches Institut, Universität Zürich, Zürich
Control of melanoma formation in vivo

Thelen Marcus | KFS 02891-02-2012 | CHF 199,800.–
Istituto di ricerca in biomedicina (IRB), Bellinzona
Role of CXCR7 in B-cell lymphoma

Thoma Nicolas | KFS 02986-08-2012 | CHF 183,100.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
The TopoIIIα-BLM-RMI1-RMI2 dissolvasome: towards a molecular understanding of a central gatekeeper of genome stability

Walter Martin | KFS 02903-02-2012 | CHF 346,200.–
Universitätsklinik für Nuklearmedizin, Inselspital, Universitätsspital Bern, Bern
A multifunctional nanoparticle platform for combined radiotherapy and targeted delivery of sirolimus

Zeller Rolf | KFS 03067-08-2012 | CHF 227,400.–
Forschungsgruppe Entwicklungsgenetik, Departement Biomedizin, Universität Basel, Basel
Functional analysis of hedgehog pathway modulation during formation of medulloblastomas: a mechanistic study with clinical relevance

Approved bursaries in 2012

Total funds allocated: CHF 446,319.–

Degrauwe Nils | MD PhD 03075-06-2012 | CHF 180,534.–
Deregulation of microRNA biogenesis in the emergence of cancer stem cells in sarcoma
Destination: Institut universitaire de pathologie de Lausanne (IUP), Centre hospitalier universitaire vaudois (CHUV), Lausanne

Meylan Patrick | MD PhD 03074-06-2012 | CHF 125,370.–
Are PPARs novel therapeutic targets for melanoma treatment?
Destination: Centre intégratif de génomique (CIG), Université de Lausanne, Lausanne

Tschuor Christoph | MD PhD 03073-06-2012 | CHF 140,415.–
Mitigation of the small-for-size syndrome through hepatic hyperplasia induced by constitutive androstane receptor agonism
Destination: Klinik für Viszeral- und Transplantationschirurgie, Universitätsspital Zürich, Zürich

Presentation of approved research projects in 2012

Aguet Michel | **Role of BCL9 proteins in regulating WNT-mediated stem cell maintenance in WNT-activated human colorectal cancer** (KFS 03022-08-2012)
Duration: 01.02.2013 – 31.01.2015

It is increasingly recognized that in addition to genetic variability, non-genetic mechanisms may contribute to the phenotypic heterogeneity observed in many tumours. Tumours such as colorectal cancers are believed to be organized, at least in part, through processes that regulate the renewal of the normal intestinal epithelium. They follow a model whereby a typically rather small proportion of undifferentiated stem cells gives rise to more differentiated tumour cells that form the bulk of the tumour. Recent evidence suggests that such cancer stem cells are often spared by commonly used therapies and are therefore responsible for tumour recurrence. Accordingly, targeting such cancer stem cells has emerged as a promising therapeutic strategy. This project proposal aims at extending our studies to human colorectal cancer cell lines and primary human tumour cultures to further validate the potential benefit of this novel therapeutic approach.

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Ballmer-Hofer Kurt | **Role of VEGF/VEGF receptor signalling in primary and metastatic tumour growth and pre-clinical evaluation of novel allosteric VEGFR-2 inhibitors** (KFS 02895-02-2012)
Duration: 01.07.2012 – 30.06.2015

Blood and lymphatic vasculature ensure the supply of organisms with oxygen and nutrients. Many diseases such as degenerative eye disease, vascular or joint degeneration, and tumour growth are accompanied by aberrantly high systemic production of vessel-promoting growth factors such as vascular endothelial growth factor (VEGF). VEGF binds and activates specific receptors expressed on the surface of endothelial cells, which form the mature vasculature. Blocking VEGF or VEGF receptors may be a means to inhibit the formation of aberrant vasculature.

We showed previously that ligand binding dimerizes and thereby alters the spatial organization of VEGF receptors. Dimerization promotes receptor activation and downstream signalling, which leads to endothelial cell migration, proliferation, and vessel formation. Based on our structural information we developed allosteric inhibitors interacting with the extracellular receptor domain. Radiolabelled variants of these inhibitors are now used to image the tumour vasculature in animal models. In addition, we will apply these inhibitors for therapeutic applications. We expect that blocking tumour vascularization in mouse tumour models will restrain tumour growth and dissemination. Taken together, our study promotes a concept for *in vivo* applications by targeting VEGF receptors for future medical diagnostics and for treating vascular pathologies.

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Becher Burkhard | **Using IL-12 in combination immunotherapy against late-stage glioblastoma** (KFS 02981-08-2012)
Duration: 01.01.2013 – 31.12.2014

Brain cancer is among the most serious forms of cancer, both in primary brain cancer and also in other types of cancer where metastases are formed within the brain. Glioblastoma is to date incurable and already leads to death 3 months post diagnosis in the majority of patients. Even aggressive surgery, radiotherapy, and chemotherapy only lead to a median survival of 12 – 15 months. Using the body's own immune system, it has been possible to treat laboratory animals in a way that a later transplanted tumour is recognized and eradicated by the immune system. However, there is virtually no data available in which an established, large brain tumour can be successfully targeted by immunotherapy.

We have discovered a method based on the combination of two independent immune signals that leads to brain cancer recognition and removal by the immune system in a murine model for glioblastoma. This therapeutic approach worked not only in early stage brain cancer but also with large, established lesions and led to tumour-free long-term survival. We are now testing this approach in other transplantable models of brain cancer in mice. Moreover, we are developing the human counterpart of the mouse-signalling molecules used in our study. Here we propose to establish the parameters to translate our findings into a clinical trial where human patients with refractory astrocytoma will be treated.

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Bentires-Alj Mohamed | **Oncogenic signalling networks downstream of PIK3CA mutations in breast cancer** (KFS 03029-08-2012)
Duration: 01.02.2013 – 31.01.2015

Each year, breast cancer is diagnosed in over one million women worldwide, and more than 450,000 lives are lost to this disease. New therapies are likely to arise from a more thorough understanding of key oncogenic signalling networks. The phosphatidylinositol 3-kinase (PI3K) pathway is frequently deregulated in human breast cancer. Activating mutations of PIK3CA, the gene encoding the catalytic subunit of PI3K, are found in 30 % of breast cancers where they activate the kinase AKT. The global changes in signalling pathways caused by PIK3CA mutations are not well understood.

Our specific aims are to: (1) assess which AKT isoforms are required for PIK3CA mutations-induced transformation *in vitro* and *in vivo*, and (2) use unbiased phosphoproteomic approaches to identify oncogenic signalling pathways downstream of PIK3CA mutations. Our studies combine both hypothesis-driven approaches and unbiased comprehensive phosphoproteomic approaches to the analysis of breast cancer models with alterations in the PI3K pathway. Our research will identify the wiring diagram of breast cancer cells with PIK3CA mutations. Our results should ultimately lead to rational implementation and/or design of targeted therapies and to the improvement of the clinical management of patients with breast cancer.

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Bodenmiller Bernd | **Single-cell signatures and signalling states during the epithelial-mesenchymal transition and their relevance for breast cancer metastasis** (KFS 03034-08-2012)
Duration: 01.01.2013 – 31.12.2015

Tumour metastases are the main cause of death in cancer patients. A process called EMT is an important factor of metastasis formation. EMT generates invasive cells that are able to disseminate throughout the body; these cells can form metastases. For many cancer types, including breast, the presence and form of EMT is still undefined and biomarker signatures describing the cellular states during EMT are absent.

Here we propose to generate quantitative, time-resolved biomarker signatures of EMT on the single-cell level to define the presence and state of EMT in mammary ductal carcinomas. Time-resolved analysis of transcripts, proteins, and cellular information processing systems of EMT will be performed in model systems to infer a comprehensive EMT signature. Then mass cytometry, which allows accurate and simultaneous measurement of up to 100 biomarkers on the single-cell level, will be used to study EMT in breast cancer at different stages. These measurements will allow, for the first time, comprehensive and sensitive detection of EMT cells in breast cancer subtypes. Correlation of these data to tumour stage and clinical information will reveal when EMT is present and the relevance of EMT for tumour development and patient outcome.

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Bourquin Carole | **Enhancing anti-cancer immunity through sequential stimulation of innate immune pathways** (KFS 02910-02-2012)
Duration: 01.07.2012 – 30.06.2014

Immunotherapy is a promising strategy for fighting cancer: The body's own defence system is harnessed to combat cancer cells. The stimulation of receptors of the innate immune system is the focus of our therapeutic approach. We demonstrated previously that certain stimuli lead to immune receptor tolerance upon repetitive stimulation, resulting in blunted immune responses and the block of further immune activation. However, all receptors do not lead to tolerance equally. We have shown that sequential administration of certain activators leads to tolerance, whereas other combinations lead to a boosted immune response.

This so-called "priming" can be translated into successful therapy of experimental tumours. In this project we investigate the mechanisms involved in this enhanced therapeutic efficacy. To this aim we perform immunological analyses in dendritic cells and macrophages to determine the modifications in signalling pathways within the cell after stimulation with pharmacological substances. The substances used in our study have already been tested in clinical trials. Thus, results gained from this project could directly impact the design of further clinical studies for the benefit of patients through enhanced efficiency or reduced toxicity of the applied immunotherapeutics.

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Chiquet-Ehrismann Ruth | **Discovery of novel genes and pathways important for cancer progression and metastasis** (KFS 02980-08-2012)
Duration: 01.02.2013 – 31.01.2015

Many cancer patients can be cured as long as their tumour has yet not spread to form distant metastases. However, if tumour cells have disseminated and metastatic foci have developed in distant organs, a cure becomes difficult, since such metastases cannot be surgically removed.

To intervene with metastasis formation, it is important to investigate the mechanism leading to the metastatic spread in the first place, to provide the basis for targeted intervention. We have found that the extracellular matrix, the substance that ties our cells together, plays an important role in this process. For example, the extracellular matrix protein tenascin-C is highly enriched in tumours, and the higher the content of tenascin-C the more likely the tumour will become invasive and metastasize. Of course, tenascin-C is not the only factor involved, and it is our aim to identify more components affecting the metastatic behaviour of tumour cells. Once identified, this will provide the basis for the development of drugs targeting these pro-metastatic factors to interfere with the process. Our project is aimed at identifying novel metastatic proteins and signalling pathways and at unravelling their mechanism of action.

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De Palma Michele | **Anti-angiogenic therapy for breast cancer: role of macrophages and microRNAs as effectors and biomarkers of tumour responses** (KFS 03007-08-2012)
Duration: 01.01.2013 – 31.12.2014

Breast cancer afflicts 1,5 million women each year and is a leading cause of mortality. Inhibiting the vascularization of tumours, a strategy called anti-angiogenesis, represents a promising anti-cancer strategy. However, breast cancer is markedly resistant to clinically approved anti-angiogenic drugs. In this regard, there is increasing evidence that immune cells called macrophages infiltrate breast tumours and limit the efficacy of such drugs. With this project, we aim to understand the biological bases of this phenomenon and identify "biomarkers" that could help us recognize signs of resistance. The ultimate goal of the project will be the development of better treatments that exploit the new knowledge obtained from the study.

We will use mouse models of breast cancer that reproduce the human disease. The first goal will be the development of strategies that target the macrophages to reduce drug resistance. To identify novel "biomarkers", we will focus on small molecules called microRNAs. By characterizing their expression in the tumours and blood of mice both before and after therapy, we may identify novel biomarkers of drug activity or resistance, which are critically needed in the clinic. A strength of this project is the ability to translate the laboratory findings rapidly to the clinic, since the anti-angiogenic drugs are currently being tested in patients.

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Gasser Susan M. | **New approaches to target the S-phase checkpoint kinase ATR** (KFS 03062-08-2012)
Duration: 01.01.2013 – 31.12.2015

The cancer genome is subject to extensive instability, which leads to an accumulation of chromosomal translocations and mutations. These can ultimately generate metastatic transformed cells from normal cells within our tissues. All organisms, from yeast to human, have common pathways that guard against genomic instability. These require a set of checkpoint signalling kinases that are activated when cells incur DNA damage. The checkpoint kinase ATR is a particularly important "guardian" of the genome, for it triggers repair, stops cell division, and stabilizes the replication fork to guarantee cell survival. Ironically, inhibitors of such checkpoint kinases are now being exploited in a novel chemotherapeutic approach that induces DNA damage in cancer cells, while inhibiting these "guardian kinases" at the same time. This double treatment enhances the death rate of cancer cells, rendering them unable to withstand DNA damage. Because cancer cells have often lost normal cell cycle controls (Rb, c-Myc) or specific repair factors (BRCA1, BRCA2), they are particularly sensitive to damage that can occur during the replication of their genomes. Our goal is to find novel co-activators of the key S-phase checkpoint kinase, ATR, and to determine its structure together with the relevant co-activators. Disruption of the activating interface between these molecules may provide new cancer therapeutics that exploit the inherent instability of the cancer genome.

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Hanahan Douglas | **Elucidating the role of tumour microenvironment in adaptive/evasive resistance and regrowth of residual disease after B-Raf driver oncogene inhibition in a mouse model of melanoma, and assessing the potential of angiogenesis and c-Met inhibitors to restrain such relapse** (KFS 03031-08-2012)
Duration: 01.01.2013 – 31.12.2015

Malignant melanoma is the cancer with the highest increase in incidence in the last decade. Recently, small molecule inhibitors have been developed against mutant B-Raf, which is mutated in 60 % of human melanoma. Vemurafenib is the first treatment in decades to show an improvement of overall survival in metastatic melanoma patients. This efficacy is limited, however: within 12 months of therapy virtually all patients relapse to progressive disease. This transitory benefit is in sharp contrast to the effects of genetic inhibition of the MAPK pathway in mouse models of melanoma. The underlying mechanisms of this discrepancy are unknown.

The aims of this study are: (1) to profile the tumour in response to genetic extinction or pharmacological inhibition of the B-RafV600E oncogene, (2) to comparatively profile the tumour microenvironment upon relapse to progressive growth following the response phase, and (3) to perform preclinical trials with mechanism-targeted drugs that combine with the B-Raf inhibitor. Our ultimate aim is that the best drug combinations identified by our preclinical studies will be advanced into clinical trials.

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Hynes Nancy | **Reciprocal cross-talk between low-density lipoprotein receptor-related protein 1 and receptor tyrosine kinases: implications for modulating *in vitro* and *in vivo* properties of breast cancer cells** (KFS 03000-08-2012)
Duration: 01.12.2012 – 30.11.2014

Breast cancer is the leading cause of cancer deaths in women worldwide. In the past decades there have been important improvements in breast cancer outcome due to innovations in surgery, screening, and therapy. These advances have had a tremendous impact on patient survival. Currently 86 % of patients diagnosed with breast cancer will be alive five years later, and if the tumour has not spread, the survival rate is 98 %. Since primary tumours are successfully removed these days, patients are concerned with their therapeutic options and with metastasis. Unfortunately, if a tumour is invasive at the time of diagnosis, the chances of metastasis increase; the tumour in the distant sites causes death.

Based on past work, we proposed that by preventing a protein named PN-1 from interacting with its receptor on breast tumour cells, we would block metastasis. We used an antibody approach for our new work and have preliminary data showing that the novel PN-1 blocking antibody does inhibit lung metastasis. We are also observing a big impact of the antibody on the tumour microenvironment. The goal of our new study is to test additional models for the effects of the antibody on metastasis.

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Imhof Beat A. | **Novel molecules for tumour treatment: angiogenesis, lymphangiogenesis, pericytes, and immune cells** (KFS 02914-02-2012)
Duration: 01.07.2012 – 30.06.2015

Tumour growth is dependent on angiogenesis, the growth of new blood vessels from the pre-existing vasculature into the tumour mass. The tumour microenvironment contributes to this pathological vascular process via a complex network of extracellular matrix molecules and various cell types. One of them is olfactomedin-like 3 (Olfml3), a secreted protein binding to the vascular growth factor BMP4 and produced by angiogenic endothelium and pericytes. Our antibodies against Olfml3 blocked short-term tumour growth in mouse models by blocking vascular sprouting and pericyte organization.

A second molecule is the enzymatic subunit NOX 1 of NADPH oxidase. This ROS-producing enzyme is expressed by angiogenic endothelium but is virtually absent from resting blood vessels. Inhibitors and gene deficiency blocked tumour angiogenesis in short-term mouse models. Using long-term tumour models we now investigate whether combinatorial therapies using inhibitors against the two molecules would block tumour angiogenesis and tumour growth more efficiently and with fewer side effects than the classical anti-VEGF treatment. To visualize tumour angiogenesis in 3D, we developed a method combining histochemistry with novel bioinformatics. This method will help us to understand the side effects on tumour vasculature, tumour invasion, and metastasis.

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Katanaev Vladimir | **Antagonists of FZD7 as anti-triple negative breast cancer agents** (KFS 02978-08-2012)
Duration: 01.02.2013 – 31.01.2015

Although triple-negative breast cancer (TNBC) constitutes about 15 % of all breast cancers, its death rate is disproportionally high. TNBC is highly aggressive and exhibits poor prognosis, as it is insensitive to conventional targeted anti-breast cancer treatments. Development of novel therapies is imperative to combat TNBC. As in many other cancers, signalling by the Wnt family of growth factors is overly active in TNBC, being one of the causes of carcinogenesis. FZD7, a Wnt receptor, is strongly overexpressed in TNBC. This study is based upon preliminary research by my laboratory that identified the switch in the type of Wnt-induced intracellular signalling (the non-canonical-to-canonical switch) as the likely causative factor of FZD7-dependent TNBC progression.

The aim of this study is to investigate the potential of reversal of this Wnt switch for suppression of TNBC cell proliferation through reintroduction of the non-canonical Wnts and development of specific small-molecule antagonists of FZD7. If successful antagonists of FZD7 capable

of preventing TNBC growth in cell culture and animal models are identified, they will become prime anti-TNBC drug candidates for subsequent detailed preclinical and clinical studies. The investigations proposed here will lay the ground for promising new anti-TNBC drugs and will hopefully contribute to a decrease in breast cancer mortality.

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Kaufmann Thomas | **Investigating the role of the Bcl-2 family member BOK in tumourigenesis**
(KFS 03014-08-2012)
Duration: 01. 05. 2013 – 30. 04. 2015

Each cell in our body is programmed to die by a highly regulated process called apoptosis. Apoptosis serves to safely remove old, unwanted, or infected cells, and importantly, it is the main mechanism for eliminating critically damaged cells that may otherwise undergo transformation and develop into cancer cells. Cancer cells typically find ways to evade apoptosis and become resistant to radiotherapy or chemotherapy. Our research focuses on the BCL-2 protein family of apoptosis regulators, including the pro-apoptotic (death-inducing) member BOK. The BOK gene is inactivated in human cancer with high frequency. BOK could thus be a "tumour suppressor", acting as guardian against cancer development.

This study aims to investigate the putative tumour suppressor role of BOK, which will be investigated in our recently developed BOK "knockout" mouse lacking the BOK

gene. We aim to translate our findings to human cancer cell lines and tumour samples. The focus is on liver cancer, colorectal cancer, and acute myeloid leukaemia, based on our previous work experience and established collaborations. We will investigate how cancer cells downregulate BOK expression, how this contributes to cancer development, and whether BOK induction constitutes a potential therapeutic strategy to help kill these cancer cells.

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Locher Kaspar | **Structural basis of inhibition of multidrug transporter ABCB1 by monoclonal antibodies** (KFS 03004-08-2012)
Duration: 01.04.2013 – 31.03.2015

Multidrug resistance continues to be a serious obstacle in cancer treatment, and drug-exporting ABC transporters play a critical role in this phenomenon. For example, the overexpression of ABCB1 (P-glycoprotein) in the cells of various tumours correlates with poor prognosis and adverse outcome for patients. We will use X-ray crystallography to study the high-resolution structure of ABCB1 in complex with inhibitory antibody fragments, which may visualize a potential Achilles heel of the drug transporter. The insights obtained may help design novel protein binders that specifically recognize ABCB1 and have altered or additional functions compared to simple antibodies. These protein binders might be fused to coloured or fluorescent reporter molecules that visualize the presence of ABCB1 with high sensitivity, thus providing novel diagnostic tools. Alternatively, they might be fused to caged drug compounds that can be activated specifically, thus providing high local drug concentrations while avoiding harmful side effects at locations where ABCB1 has a physiological role.

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Lopes Massimo | **Mechanistic insights into oncogene-induced DNA replication stress** (KFS 03028-08-2012)
Duration: 01.03.2013 – 29.02.2016

Oncogene-induced DNA replication is an important source of genetic instability in cancer cells. Although this "replication stress" is one of the earliest events in tumourigenesis, the underlying mechanisms are elusive. Our recent research on chemotherapeutics has identified fork reversal – i.e. the conversion of replication forks into four-way junctions – as an evolutionary conserved response to replication stress. Importantly, we have observed the same structures in our investigations of oncogene-induced DNA replication stress. Furthermore, we found that these structures are enzymatically processed, contributing to the genomic alterations in cancer cells. In this study we will build on this promising evidence and investigate the role of various cellular factors on the formation, maintenance, and processing of reversed replication forks. Moreover, we will exploit a system recently established in the lab to investigate re-replication, where a segment of DNA is not only duplicated once per cell cycle but multiple times. Such amplifications of genomic regions are a hallmark of cancers. We will employ standard molecular and cell biology methods and specialized single-molecule analysis of replication intermediates by fluorescence and electron microscopy. This unique combination of approaches has already provided valuable insights into other types of replication stress and thus promises to shed light on these fundamental mechanisms in tumourigenesis.

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Ludewig Burkhard | **Systems biology approach to molecularly characterize the lung cancer microenvironment** (KLS 02880-02-2012)
Duration: 01.01.2013 – 31.12.2014

Tumour cells display distinct genetic alterations that permit their unrestricted growth. In contrast, stromal cells that provide the growth scaffold and nutrients for the tumour most likely exhibit universal signatures that determine their function. The aim of this study is to gain novel knowledge on stromal cells that determine the growth-supporting microenvironment of lung cancer. Scientists and physicians at the Cantonal Hospital of St. Gallen have developed unique tools and methods for labelling, characterizing, and ablating lung cancer stromal cells. We expect that our research will identify critical target structures on lung cancer stromal cells and that this knowledge will foster the development of novel diagnostic and therapeutic avenues.

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Meylan Etienne | **Role of the antiviral innate response in the development of non-small cell lung cancer** (KLS 02885-02-2012)
Duration: 01.02.2013 – 31.01.2016

Lung cancer is the leading cause of cancer-related deaths worldwide, both in men and women. A poor response to conventional chemotherapies, a limited number of treatment options, and diagnosis at a late stage are all characteristics of this disease. Hence, a better understanding of lung cancer is urgently needed. Innate antiviral responses are activated in the organism as a defence mech-

anism against viral infectious agents. The characteristics of these responses – cell growth inhibition or cell death, induction of immune responses – are all interesting in the context of the anti-tumour response.

In this research study, we want to induce antiviral-like responses directly in mouse lung tumours *in vivo* to better understand their role in the anti-tumour response. We will also address how human lung tumour cells, grown *in vitro* in the lab, respond to the activation of those antiviral pathways. Hopefully, our study will increase understanding of the role of antiviral responses when they are triggered directly within the tumour and will contribute a basis for the elaboration of new treatments for patients with this devastating disease.

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Moreno Eduardo | **Flower^{Lose}-activated p53 and Flower^{Ubi}-activated NF-κB determine the fate of cell-competition in solid tumours** (KFS 03015-08-2012)
Duration: 01.12.2012 – 30.11.2014

Cell competition is a phenomenon responsible for cancer initiation and proliferation in the human body. Recently, the Flower isoforms Flower^{Ubi} and Flower^{Lose}, which encode calcium channels, have been shown to regulate cell competition in *Drosophila*. The Flower gene has human homologs, but their role in regulation of cell competition in humans is unknown. Also, the mechanism of Flower^{Ubi}-mediated survival of cancer cells and Flower^{Lose}-mediated apoptosis of healthy cells is unknown. Based on our preliminary data we have hypothesized that Flower^{Ubi} and Flower^{Lose} isoforms have differential ability for the uptake of extracellular calcium. The extracellular signal and source of competition is calcium, where cells with Flower^{Lose} show 6-fold higher cytoplasmic Ca^{2+} than cells with Flower^{Ubi}. Flower^{Ubi} cells undergo a NF-κB-activated survival pathway, and Flower^{Lose} cells undergo a p53-dependent apoptotic pathway. In depth understanding of the proposed mechanism will result in development of therapeutic strategies against cancer.

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Ochsenbein Adrian F. | **TRAF-binding TNF receptor signalling in leukaemia stem cells** (KFS 02879-02-2012)
Duration: 01.01.2013 – 31.12.2015

Leukaemia stem cells (LSCs) are resistant against current standard therapies, including chemotherapy and radiotherapy. Therefore, they are the main reason for leukaemia relapse. We are interested in the immune control of the LSCs. In an earlier project supported by the Swiss Cancer League, we documented in a mouse model of chronic myeloid leukaemia (CML) that CD27 signalling on LSCs induced disease progression. Therefore, blocking CD27 signalling by treatment with monoclonal antibody prolonged the time to disease progression and directly targeted LSCs. CD27 belongs to a family of TNF receptor molecules that employ the same intracellular signalling pathway. In the current project, we will analyse the impact of other members of the TNF receptor family in the development of CML. In a second step, the relevance of the signalling pathway will be analysed in a murine model of acute myeloid leukaemia and in AML samples from patients.

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Reith Walter | **Identifying the cellular functions and regulatory networks that underlie the link between microRNA-155 and cancer** (KFS 02888-02-2012)
Duration: 01.09.2012 – 31.08.2015

MicroRNAs (miRNAs) are small, evolutionarily conserved, single-stranded non-coding RNAs that inhibit the translation and/or induce the degradation of specific target mRNAs by binding to their 3' untranslated regions. Post-transcriptional regulation of gene expression by miRNAs is critical for a wide range of biological processes and implicated in various diseases, particularly in the development of diverse types of cancer. One miRNA for which a role in tumour development has been particularly well documented is miR-155.

The aim of this study is to further our understanding of the link between miR-155 and cancer by defining its normal biological functions and target genes in dendritic cells (DCs). We have demonstrated that the activation of miR-155 is a general and evolutionarily conserved feature of DCs maturation. By functional and genomic approaches, we have identified arginase 2 (Arg2) mRNA as a direct target of miR-155. Since arginase is well known for its involvement in tumour development and progression, we will assess the functional consequences of deregulated Arg2 expression in DCs and its impact on their ability to induce T-cell activation and proliferation. These studies will shed light on the mechanisms that implicate Arg2 and miR-155 in the pathogenesis and growth of cancers.

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Ruiz i Altaba Ariel | **Small molecule inhibition of WNT-TCF signalling in colon cancer** (KLS 02912-02-2012)
Duration: 01.11.2012 – 31.10.2015

Our goal is to eradicate tumour cells through the targeting of key genetic mechanisms that cancers use inappropriately. For instance, the WNT-TCF signalling pathway of intercellular communication is hyperactive in different cancers. The present project follows from our identification of small molecules that are able to specifically inhibit the WNT-TCF signalling pathway. As such, they block the proliferation *in vitro* of human colon cancer cells. In this study we propose to test the efficacy of these small molecules against colon cancer in mice. The results should allow us to envision the start of clinical trials in humans. In addition, the efficacy of these molecules will be tested also in other cancer types that depend in part on WNT signalling, such as brain (gliomas), skin (melanomas), or prostate cancers. Our current results are already very promising.

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Sartori Alessandro A. | **Identification of synthetic genetic interactions with the CtIP tumour susceptibility gene through functional RNAi screening** (KFS 03025-08-2012)
Duration: 01.03.2013 – 31.08.2015

Cancer is a class of diseases characterized by uncontrolled cell growth caused by mutations. The human CtIP protein was originally discovered as an interacting partner of three well-established tumour suppressors: CtBP, RB1, and BRCA1. Although little is known about the function of these different protein complexes, it has been shown that CtIP regulates DNA transcription and the cell cycle. In addition, CtIP is critically important for the repair of DNA double-strand breaks (DSBs), such as those induced by the DNA topoisomerase I poison camptothecin (CPT). Thus, cells which express low amounts of CtIP are hypersensitive to treatment with DSB-inducing agents. However, faithful DSB repair is crucial for genome stability, as erroneous repair can be the cause of cancer. Interestingly, the life span of mice with a heterozygous deletion of the CtIP gene is shortened by the development of lymphomas, implicating that haploid insufficiency of CtIP could be sufficient for tumour initiation.

To address the question of how CtIP contributes to tumour suppression, we aim to perform functional RNA interference screens. We will conduct these screens both in the presence and absence of CPT to identify factors required for the resistance to this chemotherapeutic drug. Collectively, our results should lead to a better understanding of the role of CtIP in tumour suppression and to the identification of novel therapeutic regimens for cancer.

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Schwaller Jürg | **Modelling and targeting of aggressive human acute leukaemia driven by epigenetic regulators** (KFS 03019-08-2012)
Duration: 01.01.2013 – 31.12.2014

Acute leukaemia is a rare cancer of the blood-forming system induced by cooperating genetic alterations. Mutations in genes encoding for "epigenetic regulators" are generally associated with a poor prognosis. Modelling of these diseases in the mouse revealed unexpectedly that gene inactivation of an epigenetic regulator led to rapid development of acute leukaemia that closely mimicked acute erythroleukaemia in patients. Although rare, acute erythroleukaemia is a severe and incurable disease in most cases, and no major genetic alteration has yet been identified.

The aim of our study is to (1) study the role of this epigenetic regulator in human acute erythroleukaemia, (2) study the molecular mechanisms of erythroleukaemia in mouse models and human cells, and (3) explore novel therapeutic strategies for acute leukaemia focusing on altered epigenetic regulators. Our work will provide insights into the molecular pathogenesis of "epigenetic" acute leukaemia that are essential to development of novel therapeutic strategies that are urgently needed to improve the prognosis of patients with these aggressive disorders.

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Skoda Radek C. | **The pathogenesis of myeloproliferative disorders** (KLS 02950-02-2012)
Duration: 01.10.2012 – 30.09.2015

The aim of our studies is to understand the molecular events that cause myeloproliferative neoplasms (MPN). MPN are blood disorders characterized by increased red blood cells, leukocytes, and platelets. MPN can progress to acute leukaemia. We identified a somatic mutation in the signalling enzyme Janus kinase 2 (JAK2) that is present in three-quarters of MPN patients. This mutation augments the enzymatic activity of JAK2, which increases the sensitivity of blood cells for incoming growth-promoting signals and thereby promotes the evolution of the disease. We now have evidence that mutations in other genes are acquired that collaborate with JAK2 in initiating MPN.

The goal of this study is to elucidate the functional role of these mutations in disease initiation and progression. One subproject focuses on familial forms of MPN that are amenable to genetic analysis. The candidate mutations that we found will be analysed for their functional consequences for growth and signalling in cell culture. We expect that these studies will advance our understanding of the molecular events that cause MPN and will allow us to develop new approaches to improve treatment of these diseases.

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Sommer Lukas | **Control of melanoma formation *in vivo*** (KFS 02897-02-2012)
Duration: 01.01.2013 – 31.12.2015

For the development of future cancer therapies it is imperative to understand the molecular processes underlying tumour initiation, growth, and metastasis formation. Many key factors involved in these processes have been identified based on cell culture and transplantation experiments, but their relevance for tumour formation and disease progression in the living organism is often unclear. Therefore, genetically modified mice spontaneously developing tumours present indispensable models for cancer research. In this study, we use a mouse melanoma model to elucidate cellular and molecular mechanisms regulating congenital nevus and melanoma formation.

We aim to tackle processes of tumourigenesis from a developmental biology point of view and based on processes occurring during normal stem cell and melanocyte development. The focus of this study is on the role of transforming growth factor beta (TGFβ) signalling in melanoma. TGFβ pathway components are essential during development and are often misregulated in human malignancies. Initial experiments in our model system indicated that *in vivo,* TGFβ is a tumour-promoting factor throughout all stages of melanoma formation, although it has previously been assumed to have tumour-suppressing activities in tumour cells grown in culture. This reveals the importance of extensive research on this and other factors in the context of the living organism, as such findings drastically influence risk assessment of therapeutic compounds and strategies for future therapies.

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Thelen Marcus | **Role of CXCR7 in B-cell lymphoma** (KFS 02891-02-2012)
Duration: 01.08.2012 – 31.07.2015

Leukocyte tumours receive marked attention in haemato-oncology. The frequency of aggressive lymphomas is about 40 % at primary diagnosis. Among these, diffuse large B-cell lymphomas (DLBCL) are the most frequent. The tumours originate from differentiating B-cells during the germinal centre reaction in lymph follicles. Several treatments are available to combat the pathology; however, several tumours appear to be resistant to therapy and a significant number of cases relapse and become resistant to the therapy. This explains the need for the development of novel therapeutic strategies. DLBCL, which arise when B-cells undergo somatic hypermutations and receptor class switching, often retain properties gained during the differentiation process and utilize these for expansion.

In this study we investigate the role of the atypical chemokine receptor CXCR7, which becomes transiently upregulated at the plasmablast stage of developing plasma cells in the germinal centres. CXCR7, which acts as a scavenger receptor, is assumed to interfere with the signalling properties of CXCR4, the functional receptor for CXCL12. CXCR4 is important for the function of germinal centres. The investigations will reveal whether expression of CXCR7 on B-cell lymphomas can be used as a clinical marker for specific subtypes and whether the receptor could be a target for therapeutic intervention.

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Thoma Nicolas | **The TopoIIIα-BLM-RMI1-RMI2 dissolvasome: towards a molecular understanding of a central gatekeeper of genome stability** (KFS 02986-08-2012)
Duration: 01.12.2012 – 30.11.2014

Cancer arises from accumulated mutations that deregulate normal mechanisms of growth control and genomic integrity. In addition to exogenous DNA damage, recent evidence argues that defects in replication also greatly contribute directly to spontaneous genomic instability. We focus on the Bloom syndrome DNA helicase (BLM) and its complexes (replication protein A (RPA), topoisomerase IIIα (TopoIIIα), RecQ-mediated genome instability protein 1 (RMI1)), which function as major gatekeepers in replication and repair. BLM and its macromolecular complexes safeguard genomic integrity in human cells. Mutations of BLM in humans result in general cancer susceptibility.

We aim to provide a molecular understanding of BLM function in health and disease. The focus will be on the BLM-TopoIIIα-RMI1/2 complex, a macromolecular machine able to dissolve Holliday junctions without introducing cross-overs. This complex, also known as the dissolvasome, thereby resolves repair and replication intermediates without loss of heterozygocity and as such maintains genome stability and counteracts oncogenic transformation. The individual molecular steps required for the coordi-

nated dissolution of converging Holliday junctions are ill-defined. We suggest an integrated approach consisting of biochemistry, structural biology, and cell biology to define the molecular interplay between the helicase (BLM), TopoIIIα, and helper proteins (RMI1/2, RPA) in Holliday junction dissolution.

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Walter Martin | **A multifunctional nanoparticle platform for combined radiotherapy and targeted delivery of sirolimus** (KFS 02903-02-2012)
Duration: 01.07.2012 – 30.06.2015

Radiopeptide therapy and protein kinase inhibition with sirolimus (rapamycin) have developed into valuable tools for treating neuroendocrine tumours. Sirolimus has shown to increase radiosensitivity in a variety of tumour tissues. We therefore aim to amplify the therapeutic effects of radiotherapy by developing nanoparticles that employ receptor targeting to deliver beta emitters (β-emitters) and sirolimus to receptor-expressing tumours. Specifically, we will design a modular tetrafunctional platform of surface modified nanoparticles to combine the following four components: (1) a nanoparticle core with an adjustable size to allow for controlling the biodistribution, (2) a surface modification for receptor targeting, (3) a metal chelator surface modification for radiolabelling, and (4) a targeted delivery of sirolimus to radiosensitize the tumour tissue. The targeting moiety on the surface of the nanoparticle platform can subsequently be changed to different receptor binding peptides or antibodies to make the probe available for imaging and treatment of various cancers.

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Zeller Rolf | **Functional analysis of hedgehog pathway modulation during formation of medulloblastomas: a mechanistic study with clinical relevance**
(KFS 03067-08-2012)
Duration: 01.01.2013 – 31.12.2014

Medulloblastomas are among the most aggressive brain tumours in children, and the best therapy is a combination of surgery with radiation therapy and/or chemotherapy, which often results in long-term damage, as the brain is still developing. Fortunately, there are several mouse models to study medulloblastoma formation, and in particular, Ptch1 heterozygous mice have made it possible to identify and characterize the molecular changes that underlie one of the most common medulloblastoma subtypes. We have shown that two naturally occurring signal modulators are produced in abnormally large amounts by medulloblastoma cells and are now analysing how this alters normal development.

In particular, we are interested in understanding how these two factors, the protease-inhibitor SerpinE2/PN-1 and the BMP signal inhibitor Gremlin1, facilitate medulloblastoma development in mice. In addition, we have developed cellular models to be able to manipulate the molecular mechanisms and interactions. Functional analysis in mice and cellular models is combined with analysis of human medulloblastoma biopsies. These studies should produce insights into medulloblastoma formation and help us to design strategies to interfere with these extracellular factors. We hope that their concurrent inhibition will allow us to disrupt tumour development without inducing rapid tumour resistance.

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Further approved research project in 2012

Peter Matthias | KLS 02906-02-2012 | CHF 243,100.–
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Characterization of the human MMS22L-TONSL complex in maintenance of genome stability and prevention of carcinogenesis

Research trends in radiation therapy

On 8 November 1895 Wilhelm Conrad Röntgen discovered new rays, to which he gave the name X-rays; in many languages they were later called Röntgen rays in his honour. Radiation therapy was founded as a new scientific field with the publication of an article by Leopold Freund ("Ein mit Röntgen-Strahlen behandelter Fall von Naevus pigmentosus piliferus") in the *Wiener Medizinische Wochenschrift* on 6 March 1897. At the end of 1896 Freund had treated a five-year-old girl with a naevus pigmentosus piliferus that covered a large surface of her back (a benign, large, brown-pigmented alteration of the skin) with three sessions of radiation and delivered evidence of the biological effectiveness of X-rays. As early as in 1903 Freund published the world's first textbook on radiation therapy, *Grundriss der gesamten Radiotherapie für praktische Ärzte (Elements of General Radio-Therapy for Practitioners)*.

Numerous scientific works and groundbreaking achievements in the field of radiation biology and radiation physics followed. Parallel to this was the technological development of more efficient X-ray tubes, telecobalt units, and circular accelerators, thanks to which over time also radiation treatment of altered tissues deep inside the body became possible. This laid the foundation stone for radiation of malignant tumours, and radiation of benign changes (tumours that compress but do not invade neighbouring tissue or metastasize) receded more and more into the background. Very early on there was recognition of the potential dangers of radiation, such as dose and volume-dependent acute toxicities of irradiated tissues (for example, inflammation), possible long-term effects (for example, scarring), and the risk of radiation causing secondary tumours.

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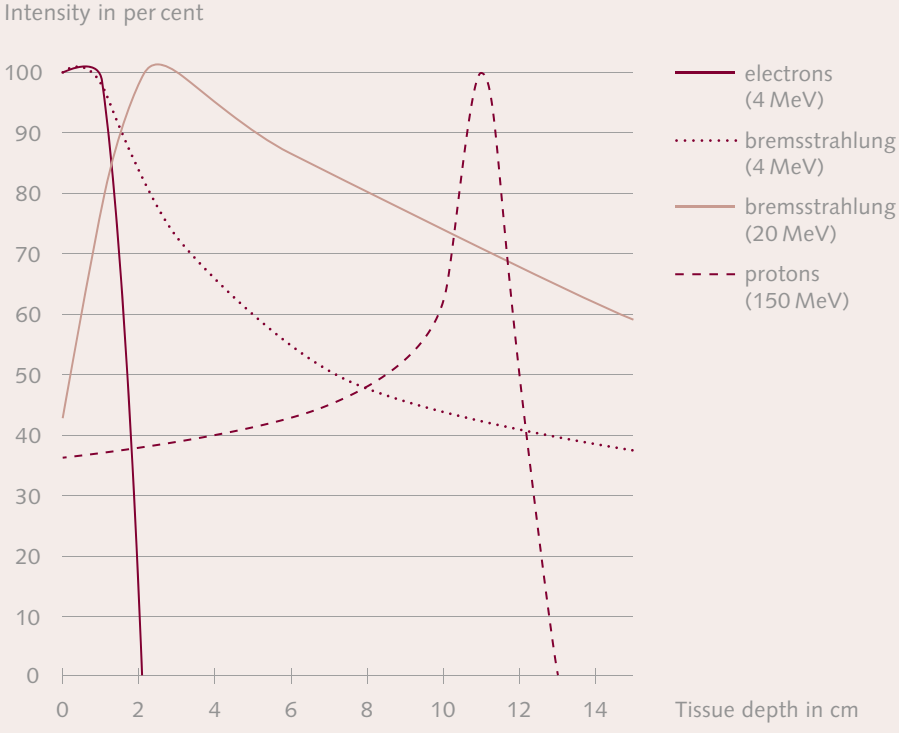
Electrons or photons for tumour treatment

For percutaneous radiotherapy – external beam radiation therapy from the outside to the inside through the skin – linear accelerators are used almost exclusively in Switzerland. The linear accelerator generates electrons and then speeds them up to almost the speed of light using electrical fields. These electrons are used to treat areas that are on, or close to the skin's surface or are fired at a metal target made of tungsten. This decelerates or "brakes" the electrons, and the resulting bremsstrahlung (emitted as photons) has a higher penetration depth than the electrons. The greater the energy of the photons, the deeper the radiation can penetrate the body (Figure 1). When these high-energy photons enter the patient's body, they aim to break the cellular biomolecules, in particular the DNA in all the cells within the treatment field. If the cells are unable to mend the numerous DNA damages, they cannot reproduce or they die.

Although the radiation works only locally on the radiated body cells, it affects not only cancerous cells but also normal tissue. Healthy cells usually have better repair mechanisms to mend themselves of the damage caused by the radiation. To exploit this char-

Figure 1
Depth dose curves: Different tissue penetration depths of photons (4 MeV; 20 MeV), electrons (4 MeV), and protons (150 MeV) (© 2008 Free Software Foundation)



acteristic, the total dose of the radiation of the affected body regions is often spread out over time, in fractions (fractionation). Radiation treatment planning defines the dose, how many radiation beams to use, and which angles each will be delivered from. Care is always taken to consider the tolerance dose to surrounding healthy structures.

Greatest possible effect with smallest possible damage

Some medical centres also provide brachytherapy, or short-distance therapy, where a radiation source is placed directly inside or next to the tumour. This is internal radiation therapy. The hope is to reduce the exposure to radiation of surrounding healthy tissue, which is always affected in radiation therapy at least to some degree. Due to the small range, this type of radiation can be used only in certain situations. One example is the use of radioactive (iodine) seed implants in treatment of prostate carcinomas.

In sum the following can be stated: The higher the dose of radiation of cancerous tissue, the greater the destruction of the tumour. And the higher the dose applied to the surrounding healthy tissue, the greater the risk of serious treatment side effects. The more targeted the radiation is to the tumour, the more that damage to surrounding healthy tissue is minimized and the lower the risk of the side effects. In this way, it can be possible to increase the individual fraction sizes and shorten the total treatment time, thus improving patients' quality of life.

A large part of the current research trends in radiotherapy are based on these considerations. A few of those trends are presented in the following.

New positioning and positioning aids

The position for standard treatment of the female breast is the supine position, with patients lying on their backs, and with treatment fields that slightly touch the body. Here, inclusion of the lung and, to a lesser degree, the heart is often unavoidable. Some institutes have begun to radiate patients in a prone position. In the prone position and with a gap between the positioning aid, gravity pulls breast tissue away from the body, which often results in less radiation dose to the lungs and heart.[1] In our experience at our institute, patients with large breasts profit the most from prone treatments.

Imaging methods for radiation planning and control

As it becomes possible to conduct radiation treatment to submillimetre precision, there is an increased necessity for imaging of the exact shape of the tumour (target volume) and for treatment planning. Highly complex imaging techniques are used here. In addition to magnetic resonance imaging (MRI) and NMR spectroscopy, mainly positron emission tomography (PET) and a new imaging tool that combines positron emission tomography with computed tomography in one scan (PET/CT) are becoming more important. The integration of these techniques allows the tumour volume to be precisely delineated from healthy tissue. In addition, it standardizes the area to be radiated, as in many cases radiologists define the area somewhat differently. PET also delivers detailed information on the tumour biology, according to which the response to treatment can be monitored and, if needed, the radiation dose adapted to the biological behaviour of the tumour.[2] A lot of research activities are dealing with these imaging tools and systems and are investigating the use of different radioactive tracers with different types of tumours.

Complex methods of more precise radiation

With intensity-modulated radiation therapy (IMRT), the intensity of the radiation beam is modulated – or controlled, meaning deliberately made non-homogenous. Typically, combinations of multiple intensity-modulated fields coming from different beam directions allow radiation of the structures with complicated shapes also when they are in immediate proximity to healthy, sensitive organs at risk. For some radiation treatments, for example for tumours in the head and neck or for prostate carcinomas, this method is now used routinely at many radiation oncology institutes. A further development of the principle is volumetric intensity modulated arc therapy (VMAT), a new method whereby radiation is delivered by rotating the gantry of a linear accelerator through one or more arcs with the radiation continuously on. This allows even better adaptation of the dose delivered to the target volume (Figure 2).[3] The same applies to tomotherapy. Intensive research is currently investigating the specific advantages to patients with these new radiation methods.

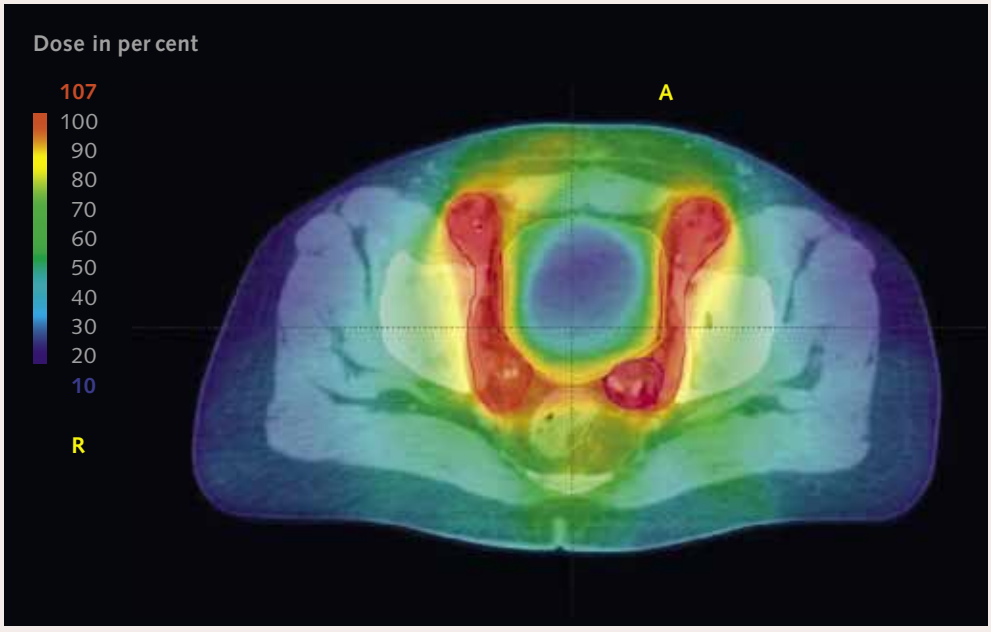
New types of radiation, such as protons and heavy ions

Protons are positively charged parts of atoms that can also be used for radiation therapy. Proton beam radiation therapy requires more highly specialized

Figure 2

Volumetric intensity modulated arc therapy (VMAT): Highly precise, intensity-modulated rotational radiation therapy

Transversal dose distribution for radiation of affected lymph node regions near sensitive organs at risk in the pelvic region



and more expensive equipment than photon/electron therapy. The advantage of protons lies in their physical characteristics: Protons are the most effective deep in the body at the end of their path and cause fewer side effects to surrounding normal tissues (Figure 1). This makes proton radiation the treatment of choice for certain tumours such as uveal melanomas, tumours that occur in the eyes. Switzerland has one of the most renowned proton centres in the world, the Paul Scherrer Institute (PSI). The extent of the advantages of proton radiation over photon radiation for common cancers needs to be investigated in clinical studies. Recently published findings did not find proton radiation advantageous as compared to IMRT for localized prostate carcinoma.[4] Also interesting for radiation therapy are heavy ions (for example, carbon ions ^{12}C), which have higher biological effectiveness than photons or protons. The Heidelberg Ion-Beam Therapy Center, which opened in Heidelberg, Germany, in 2009, is the only centre worldwide for heavy ion therapy (helium, oxygen, and carbon ions) as well as proton therapy.

Radiosensitization of the tumour tissue

The question that probably most of current research activities are examining is the following: How can tumour cells be made more sensitive to radiation? A host of possible molecular targets and agents with targeted effects are being studied in combination with ionizing radiation. The challenge is to make the right choices for further development in clinical application. The identification of factors that can predict the radiation effect would be enormously important for individualization and personalization of radiation therapy.[5] A further method that can be used to make tumour cells more sensitive is exposing tumour tissue that is to be radiated to high temperatures. Researchers hope to find promising results from hyperthermia used with radiation therapy.

Radioprotection of normal tissue

Another approach is to make healthy tissue less sensitive to radiation. An example is the drug amifostine, which is used to protect the paratid glands, or selenium to prevent radiation-induced side effects (inflammation of the small intestine) of radiation treatment of gynaecological tumours. To protect healthy cells, many patients take free-radical scavengers and antioxidants, but radiologists have concerns that antioxidants may possibly also protect cancer cells from damage caused by radiation therapy.

Radiation therapy during surgery

Radiation therapy given during surgery is called intraoperative radiation therapy (IORT). It is rather complex and has been conducted only at a few radiation oncology clinics, for example for treatment of pancreatic cancer, soft tissue cancer, or recurrences of rectal cancer. The method has received new impetus through its use for breast cancer. For certain patients, several weeks of radiation therapy after surgery could be replaced by one concentrated dose of radiation therapy delivered to a tumour bed during surgery. After studies that yielded some initially comparable results, more current studies are finding that IORT alone leads to a slight increase in local recurrence.[6] Further research results are needed.

High-precision irradiation with radiosurgery

The number of research publications on radiosurgery has increased in the past few years. Radiosurgery is a highly precise, intensified form of radiotherapy. It delivers a single, very high dose fraction of radiation, thus imitating surgery, so to speak. Ideally, the tumour should have very well-defined edges, which unfortunately is often not the case. Most often used for brain tumours, this method, sometimes robot-aided, can also be used outside the brain in fractions; this is called extra-cranial stereotactic radiotherapy

(ESRT). New data show that outcomes up to now of radiosurgery/ESRT for some types of tumours are comparable to the outcomes of surgical operations, for example for small lung tumours.[7] The method is also being used in the re-irradiation situation.[8]

Standardization of methods

There is hope that current research trends in radiation therapy will contribute towards local tumour destruction and thus improved survival rates for many patients. Many of the technological achievements mentioned above also aimed and still aim to reduce side effects and in this way to improve patients' quality of life. We radiation oncologists of course do not want to withhold these developments from patients, even if there is a lack of comparative clinical studies. However, it is becoming more and more difficult to conduct such research studies, because funding of purely radiation-oncology questions is often not considered a priority. With the increasing possibilities of image-guided radiotherapy and ever more sophisticated application techniques, there is a growing need for some standardization and harmonization of methods, also within Swiss radiation therapy centres, which does not mean there should be any loss of consideration of the individual situation of each patient with cancer. This is a task especially for the Society of Swiss Radiation Oncologists.

PD Günther Gruber, MD

Günther Gruber studied medicine at the University of Innsbruck in Austria. From 1994 to 2000 he was a resident in general surgery at Brugg District Hospital and in radio-oncology at Cantonal Hospital Aarau and Bern University Hospital (Inselspital). He stayed in Bern up to 2005, first as deputy senior physician, then senior physician, and then became consultant in charge of the Radio-Oncology at Cantonal Hospital Aarau. Two years later he became head of the Institute for Radiotherapy Zurich, which is a part of the Hirslanden private clinic group. Gruber has long been active in clinical research, with a focus on optimization of radiation therapy for breast cancer. He has been president of the Society of Swiss Radiation Oncologists (SRO) since 2008.

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List of completed research projects in 2012

Anderle Pedone Pascale | OCS 02303-08-2008 | CHF 195,000.–
Institut für Biochemie und Molekulare Medizin, Universität Bern, Bern
Exploiting transporters in the tumour-stroma interface to aim for a more efficient chemotherapy

Baudis Michael | KLS 02179-02-2008 | CHF 170,800.–
Institut für Molekulare Biologie, Universität Zürich, Zürich
Oncogenomic pattern detection in B-cell non-Hodgkin's lymphomas for pathway description and disease classification

Bourquin Jean-Pierre | KFS 02453-08-2009 | CHF 125,500.–
Abteilung Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Pre-clinical evaluation of a new pharmacological approach using obatoclax for chemosensitization of drug resistant childhood acute lymphoblastic leukaemia

Bourquin Jean-Pierre | KFS 02583-02-2010 | CHF 238,000.–
Abteilung Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Comprehensive analysis of the cell surface proteome of childhood refractory ALL for identification of new diagnostic and therapeutic targets

Dirnhofer Stephan | OCS 02072-04-2007 | CHF 240,400.–
Institut für Pathologie, Universitätsspital Basel, Basel
Prognostic and predictive significance of recurrent genetic aberrations and cellular differentiation and cell cycle control markers in diffuse large B-cell lymphomas (translational research of the SAKK 38/07 study)

Gautschi Oliver | KLS 02164-02-2008 | CHF 218,200.–
Medizinische Onkologie, Luzerner Kantonsspital, Luzern
Regulation of ID1 expression by Src in cancer: clinical implications

Heim Markus Hermann | KLS 02522-02-2010 | CHF 218,300.–
Klinik für Gastroenterologie und Hepatologie, Universitätsspital Basel, Basel
Hepatocarcinogenesis in chronic hepatitis C

Heinimann Karl | KFS 02489-08-2009 | CHF 133,000.–
Forschungsgruppe Humangenetik, Departement Biomedizin, Universität Basel, Basel
miRNA expression profiling in Lynch syndrome-associated colorectal cancer

Nadal David | KLS 02375-02-2009 | CHF 227,900.–
Abteilung Infektiologie und Spitalhygiene, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Is endemic Burkitt's lymphoma really promoted by chronic innate immunity triggering by malaria infection?

Renevey Philippe | KFS 02681-08-2010 | CHF 138,400.–
Centre suisse d'électronique et microtechnique (CSEM), Neuchâtel
Automatic vocal aid system for laryngectomees with improved voice quality

Resink Thérèse | KFS 02447-08-2009 | CHF 343,000.–
Labor für Signaltransduktion, Departement Biomedizin, Universitätsspital Basel, Basel
T-cadherin: a functional determinant and early prognostic marker for malignant transformation of squamous cell carcinomas

Rothermundt Christian | KFS 02641-08-2010 | CHF 76,500.–
Fachbereich Onkologie/Hämatologie, Kantonsspital St. Gallen, St. Gallen
Metformin in castration-resistant prostate cancer: a multicentre phase II trial conducted by the Swiss Group for Clinical Cancer Research (SAKK 08/09)

Skoda Radek C. | KLS 02398-02-2009 | CHF 324,100.–
Experimentelle Hämatologie, Departement Biomedizin, Universitätsspital Basel, Basel
The pathogenesis of myeloproliferative disorders

Zeller Rolf | OCS 02368-02-2009 | CHF 360,350.–
Forschungsgruppe Entwicklungsgenetik, Departement Biomedizin, Universität Basel, Basel
Functional analysis of modulators of SHH pathway activity during the formation of medulloblastomas: a mechanistic study with clinical relevance

Clinical research

Presentation of completed research projects in 2012

Anderle Pedone Pascale | **Exploiting transporters in the tumour-stroma interface to aim for a more efficient chemotherapy** (OCS 02303-08-2008)

Tumour cells within the same carcinoma are heterogeneous and contribute to different aspects of tumour progression. Whereas some are mainly responsible for tumour growth and are in a proliferating state, others at the invasive front are responsible for invasion into the surrounding tissue. It has become clear in recent years that the behaviour of a tumour does not depend solely on the tumour cells alone but also on the interaction of the tumour cells with the surrounding tissue. However, still little is known about how tumour cells respond to their microenvironment. A better understanding of the underlying processes could eventually lead to improved therapy.

In this project we studied the expression and functions of membrane transporters, which are known or very likely to be involved in tumour progression and may also serve as drug carriers. Using laser-dissection microscopy of tumour and healthy colon tissue from freshly operated patients, RNA was extracted to perform genome-wide profiling.

In addition, we examined the direct effect of transporters on tumour cells. As a result of the changed needs during cancer progression, transporters, which account mostly for the active transport of metabolic molecules, are differently expressed. Some transporters are upregulated in tumour cells due to the increased demand of energy and nutritional needs. This renders SLCs potential targets in the treatment of cancer. Indeed, we have observed that loss of expression of some transporters had a significant impact on cell viability.

In general, tumour-stroma interaction is still an emerging field of study. In particular, the expression of transporters has hardly been studied in the context of tumour-stroma interaction or in the context of the heterogeneity of a solid tumour. Thus, a better understanding of the role of transporters with respect to chemosensitivity and resistance in the various tumour cell subpopulations will contribute to more efficient chemotherapy.

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Baudis Michael | **Oncogenomic pattern detection in B-cell non-Hodgkin's lymphomas for pathway description and disease classification** (KLS 02179-02-2008)

Malignant B-cell lymphomas (B-NHL) are a group of neoplasias with a rapidly increasing incidence, the reasons for which have been poorly understood so far. The last decades have seen major progress in the therapy of some lymphoma variants, in part due to the introduction of improved chemotherapy protocols and supportive measures. Additionally, some types of B-NHL now can be treated with targeted approaches, e. g. based on cell type-specific antibodies. However, in recent years it has become evident that for some lymphoma variants, progress has been limited so far and that a deeper understanding of the disease biology is needed to achieve better therapeutic results.

The malignant transformation of human cells is the result of a selective accumulation of genomic mutations, which lead to cancer development by promoting increased proliferation and limiting the controlled cell death (apoptosis) of aberrant cells. Although we now understand that some types of mutation are specific for individual cancer types, we are also beginning to learn something about the importance of individual mutation profiles for disease classi-

fication and clinical risk prediction. For a better understanding of these complex dependencies, large amounts of genomic data as well as tailored bioinformatics methods are needed.

As part of our project, we were able to assemble a collection of genomic copy number profiles from more than 5,300 malignant B-NHL. We developed a new biostatistical method, "CDCOCA", which can be used to explore the statistical significance of co-occurring genomic aberrations in individual tumours, based on large oncogenomic data collections. With this method, we were able to delineate e. g. TNF-alpha and TCR-mediated signalling cascades as potential mutation targets in mantle cell lymphomas. In an analysis that went beyond lymphoma genomics, we showed that specific regional genome amplifications and deletions display a statistical association with selected cancer entities.

These results, and especially the extensive data collections and bioinformatic tools that they are based on, represent important advances in our understanding of the biology of malignant B-cell lymphomas but are also suitable for the exploration of other cancer entities. The genomic profiling data and associated clinical data have been made available through our "Progenetix" online database project at www.progenetix.org to be used by interested research scientists and physicians.

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Bourquin Jean-Pierre | **Pre-clinical evaluation of a new pharmacological approach using obatoclax for chemosensitization of drug-resistant childhood acute lymphoblastic leukaemia** (KFS 02453-08-2009)

Aims

Using a preclinical model that is based on representative cases with highly resistant disease, we aimed at establishing new approaches for chemosensitization in acute lymphoblastic leukaemia (ALL).

Experimental approach

Using samples from patients with resistant disease, we built a preclinical testing programme based on xenotransplantation in immunodeficient mice. We tested new agents that target the regulation of programmed cell death to evaluate their potential to act as chemosensitizer.

Results

A small molecule that is thought to act as an antagonist of critical regulators of programmed cell death, obatoclax mesylate, very effectively restored the response to conventional chemotherapeutic agents in ALL cells that were otherwise completely refractory to these conventional chemotherapeutic agents. Unexpectedly, combination of obatoclax with dexamethasone, one of the most important drugs for ALL treatment, triggered a new type of programmed cell death specifically in resistant leukaemia cells but not in chemosensitive ALL cells, providing a strong rationale for a selective therapeutic targeting of resistant leukaemia cells. Interestingly, combination of obatoclax with other cytotoxic agents triggered a classical cell death pathway, the mitochondrial apoptotic pathway, suggesting that this agent interferes with critical mechanisms at the interface of two cell death pathways.

We have now established an automated imaging based platform for rapid screening of drug activity in co-cultures of leukaemia cells from patients on stromal support cells from the bone marrow. This allows us to test the drug sensitivity profiles of patients effectively. Obatoclax is generally active on samples from patients with resistant disease. We could not find any case that would not respond to the combination of obatoclax with chemotherapeutic agents in B-cell precursor-ALL but have detected several resistant cases in T-cell ALL. Sensitization activity to the glucocorticoid drug dexamethasone using obatoclax was clearly associated with inhibition of mTOR kinase activity, an important signalling node that integrates signals from different pathways to promote tumour growth. Our data suggest that the modulation of this pathway is an important component of the response to the combination treatment of obatoclax with glucocorticoid drugs.

We established a method to detect this activity in leukaemia cells directly *in vivo,* which is an important aspect for the development of a clinical trial. We consistently detected reduction of mTOR kinase activity in leukaemias that responded to treatment but not in leukaemias that were resistant to this approach. It will therefore be possible to obtain direct evidence for biological activity of drug combination in patients under treatment with obatoclax and dexamethasone, which is relevant in order to determine the dosage in the clinical setting. Further, the identification of independent ALL cases that were resistant to obatoclax-mediated chemosensitization provides a strong basis to better understand the molecular mechanisms that are involved for drug activity.

Implications for clinical translation

We established a new rationale to achieve chemosensitization using a preclinical model that is representative of the patient population at need. We submitted a proposal for a clinical trial, which was well received by the international study group. We are now dissecting the molecular mechanisms that are involved in mediating this type of treatment response. This study illustrates the potential of preclinical testing to tailor combination treatment more individually. We hope that this type of approach will contribute to improving the dismal outcome of patients with refractory disease and serve to reduce treatment in general.

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Bourquin Jean-Pierre | **Comprehensive analysis of the cell surface proteome of childhood refractory ALL for identification of new diagnostic and therapeutic targets** (KFS 02583-02-2010)

Aim

Acute lymphoblastic leukaemia (ALL) of childhood is a deadly disease for which salvage of therapy-resistant cases remains challenging. Leukaemia-associated cell surface markers have been very useful for leukaemia classification, and may provide better possibilities for selective therapeutic intervention. Here we exploit the power of combining two experimental platforms to generate an unprecedented view at the cell surface landscape in childhood ALL, and identify potential leukaemia-associated markers.

Methods

We have established a reliable methodology to expand small amounts of leukaemia cells directly from patient samples, while keeping the dominant genetic and phenotypic features of the original leukaemia. We are now in a unique position to perform biomedical studies that were previously deemed impossible due to limiting material. In collaboration with the Institute for Systems Biology at the ETH Zurich, we have mapped hundreds of cell surface proteins on leukaemia cells from patients with highly resistant or very chemosensitive disease. We took advantage of a proteomic technology that relies on the specific tagging of cell surface proteins on specific sugar structures on the protein backbone directly on the surface of intact living cells. Small peptide fragments can then be purified based on the presence of such a tag and analysed simultaneously using mass spectrometry, a technique that enables to determine the protein composition in a large mixture that is obtained from cellular preparations after the identification of these protein fragments.

Results

We determined the cell surface proteome of 20 ALL cases. The proteomics-based approach completely recapitulated the typical pattern of leukaemia-associated markers for ALL classification, as it is usually analysed by multicolor flow cytometry at diagnosis in the clinical setting. Using filtering strategies that integrate gene expression profiling data from normal components of the blood development in humans, we identified cell surface proteins that are different in their expression levels compared to the non-malignant cell populations in the bone marrow. This list of candidate markers is enriched for markers that are found in very early stages of the blood development, indicating that they could constitute interesting targets for therapeutic interference. We have validated several markers in the clinical setting for their value to identify leukaemia cells in bone marrow samples. This work has been submitted for publication. By comparing samples from patients with very resistant disease and from patients with very good outcome, we also identified a set of cell surface

markers that predict disease relapse in a subset of the patients in the setting of our international clinical treatment protocol. We are now evaluating the function of these cell surface proteins more closely and are investigating which underlying genomic abnormalities are associated with this important feature of the disease.

Clinical relevance

Taken together, the combination of the mouse xenograft model of ALL with modern proteomic technologies provides a view of the leukaemia cell surface with an unprecedented resolution. A number of applications will be derived from this knowledge base. A significant contribution will be the identification of a new prognostic marker in ALL that we expect to provide new insights in disease pathogenesis. The identification of this new prognostic subgroup in ALL has relevant implications for clinical translation.

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Dirnhofer Stephan | **Prognostic and predictive significance of recurrent genetic aberrations and cellular differentiation and cell cycle control markers in diffuse large B-cell lymphomas (translational research of the SAKK 38/07 study)** (OCS 02072-04-2007)

Study outline

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma in humans. By the use of the currently most effective therapeutic strategies about 60 % of the patients can be cured. Unfortunately, up to now it has not been possible to use specific biological features of tumour cells (biomarkers) to assess individual patients' prognosis or to predict their response to therapy. We analysed a collective of DLBCL patients who were treated in a clinical study (Prognostic and predictive significance of recurrent genetic aberrations and cellular differentiation and cell cycle control markers in diffuse large B-cell lymphomas, SAKK 38/07).

Study design

Our main objective was to identify prognostic and predictive biomarkers in DLBCL patients. The primary endpoint was event-free survival at 2 years (2yr EFS).

Methods

We prospectively analysed the expression of various biomarkers using immunohistochemistry in 123 patients with DLBCL. In addition, genetic alterations of the BCL2 gene and the C-MYC gene were analysed by fluorescence *in situ* hybridization (FISH). The results were correlated with clinicopathological parameters and the clinical course of the patients.

Results

The medium patients' age was 59 years; 68 % were men. BCL2 gene breaks were observed in 9 % and C-MYC breaks in 8 % of the cases. Only one-third displayed C-MYC/IGH fusions. Median follow-up was 33 months, median EFS was not reached; 2yr EFS was 56 %. Molecular factors linked with 2yr EFS were expression of CD5, cyclin E and BCL2, or C-MYC gene rearrangements.

Patient benefit

Despite recent progress in the therapy of DLBCL by immunochemotherapy, up to 40 % of the patients show a relapse. Thus, it is important to identify these patients already during first diagnosis of their disease to optimize treatment strategies from the start. Besides clinical factors, tumour-specific factors (biomarkers) are considered important. We identified four biomarkers (CD5 and cyclin E protein expression, translocation of the BCL2 or C-MYC gene) which are associated with a worse prognosis.

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Gautschi Oliver | **Regulation of ID1 expression by Src in cancer: clinical implications** (KLS 02164-02-2008)

Introduction

The project addressed the molecular biology of tumour cell invasion and metastasis, focussing on factors that modulate the activity of a new class of anti-cancer drugs and that may serve as predictive biomarkers in the clinic.

Aims

Invasion and metastasis are a hallmark of cancer, and the underlying molecular mechanisms provide opportunities for new therapies. Two signalling pathways have a pivotal role in the regulation of invasion and metastasis: the transforming growth factor (TGF) pathway, and the Src kinase pathway. Src kinase inhibitors are in clinical development; however, their optimal use in oncology remains to be defined. Previous work by the project leader at the University of California showed that the TGF and Src pathways converge in the regulation of the stem cell gene ID1. This study addressed the question of how Src regulates ID1 and whether ID1 could be a biomarker for Src inhibitors.

Methods

In the Laboratory of Oncology at the Bern University Hospital, Oliver Gautschi's group studied the Src-ID1 signalling pathway in lung cancer. Expression of Src and ID1 was analysed in archived primary lung cancers by immunohistochemistry. Microarrays were performed to identify microRNAs (miRs) involved in the Src-ID1 pathway. Candidate miRs were further tested in cancer cell lines by using lentiviral vectors, invasion assays, and incubation with Src inhibitors. Mouse experiments were conducted to generate preliminary *in vivo* data.

Results
Many of the lung cancers examined had highly elevated ID1 levels, which was associated with poor prognosis in patients. Cell line experiments revealed ID1 to be a novel target of miR-29 and miR-381. Expression of miR-29 and miR-381 inversely correlated with ID1 expression in primary lung cancers. These two miRs through ID1 were implicated in the myc signalling pathway and modulated the activity of Src kinase inhibitors in lung cancer cell lines. Preliminary results from experiments with mice carrying tumour xenografts suggested that this effect could be relevant *in vivo*.

Conclusion
Based on this study, further research is justified to validate these novel biomarkers in patients with advanced cancer treated with Src inhibitors.

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Heinimann Karl | **miRNA expression profiling in Lynch syndrome-associated colorectal cancer**
(KFS 02489-08-2009)

Colorectal cancer (CRC) is among the most common cancer types in the Western world. Up to 20 % of CRCs have a hereditary basis, with Lynch syndrome representing the most common cancer predisposition worldwide. Although the genetic basis of Lynch syndrome (LS) is well-known, medical management of carriers remains difficult, in particular with regard to disease development, prognosis, and cancer prevention.

In this study we assessed how CRC development in LS may be influenced by microRNA (miRNA) expression. miRNAs are short RNA molecules that control about 30 % of all genes in humans. Following extensive standardization and employing latest molecular genetic analysis methods, we identified 703 miRNAs that were differentially expressed in LS compared to sporadic tumours.

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Nadal David | **Is endemic Burkitt's lymphoma really promoted by chronic innate immunity triggering by malaria infection?** (KLS 02375-02-2009)

Endemic Burkitt's lymphoma is a particular cancer of lymph nodes in Africa. The cancer cells harbour Epstein-Barr virus (EBV), a virus that infects more than 90 % of children and adolescents and subsequently remains in the host for a lifetime. This type of cancer develops in regions where malaria is endemic. Therefore, malaria is believed to essentially contribute to the development of endemic Burkitt's lymphoma.

Study design
We aimed to expand on and deepen our previous work suggesting that stimulation of the innate immunity in a similar fashion as malaria impacts on EBV, thereby promoting its form that induces unrestricted proliferation of lymph node cells.

Study goal
Exploration of three essential steps in the development of cancer harbouring EBV: Effects of chronic stimulation of the innate immunity on (1) preservation of the EBV form that promotes survival of cells (latent EBV), (2) EBV-induced survival of cells, and (3) cell proliferation fuelled by EBV.

Methods and procedure
We stimulated the innate immunity of cells from endemic (with EBV) and non-endemic (without EBV) Burkitt's lymphomas, respectively, in a similar fashion as malaria and recorded the behaviour of EBV and of cancer cells in relation to their harbouring EBV or not. In addition, we generated cells harbouring given single structures of EBV to identify essentially involved parts of the virus.

Results
We showed that stimulation of cancer cells in a similar fashion as malaria preserved the form of EBV that promotes the survival of cells. Further, we unravelled a change in the packaging of EBV-DNA within the host cell as the responsible mechanism, the essential part of EBV, and in part the signalling pathway within the cell after its stimulation. Moreover, we showed that agents stimulating the innate immunity to improve cancer treatment that are already used in studies have an unpredictable impact on the survival of lymph node cancer cells, if they stimulate the cells in a similar fashion as malaria. The effect is independent of the presence or absence of EBV.

Recommendations and patient benefit
The deciphering of the interaction between stimulation of the innate immunity and the behaviour of EBV-harbouring cells towards the development of cancer provides an important basis to engineer novel methods for the prevention and treatment of EBV-harbouring lymph node cancer. The effects of agents to stimulate the innate immunity on cancers cells need to be tested for the individual patient before they can be prescribed.

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Renevey Philippe | **Automatic vocal aid system for laryngectomees with improved voice quality**
(KFS 02681-08-2010)

The scope of this project is the construction of a system to record the voice of these people, to process it, and to reproduce in real-time a restored version. The final goal is to improve the patients' quality of life and their social interactions.

Current methods of signal processing allow to separate, from a recording, the excitation signal (the vibration of the vocal cords) from the resonances of the vocal tract produced by the movements of different articulators (jaws, tongue, and lips). In the case of pathological voices only the excitation source is affected by the surgery. In order to improve voice quality this signal can be processed to be closer to the characteristics of a healthy voice and then combined with the articulatory parameters to synthesize a voice that preserves as much as possible the original voice specificities (before laryngectomy).

Conventional methods based on a model of healthy voice give poor performances when applied to voices after laryngectomy. The main objective of this project was therefore to improve existing methods and develop new methods that take into account the specificities of pathological voices. This study focuses on the problem of decomposition of the signal, which is one of the key points to get a good quality of voice restoration.

The results showed a significant improvement in performance over conventional methods. However, it should be emphasized that these performances are dependent on the quality of the residual voices after the operation. Good performances are obtained with voices resulting from partial laryngectomy. However, substitution voices acquired after a total laryngectomy do not obtain satisfactory results at present.

This study made possible the development of new methods of signal processing to better understand and treat the specificities of pathological voices. This represents a significant step towards the implementation of these methods for a real-time portable device. Nevertheless, some issues still have to be resolved.

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Resink Thérèse | **T-cadherin: a functional determinant and early prognostic marker for malignant transformation of squamous cell carcinomas** (KFS 02447-08-2009)

Squamous cell carcinoma (SCC) is a type of skin cancer. There are two main types of skin cancer: melanoma and non-melanoma. SCC is a non-melanoma skin cancer and the second most common type of skin cancer. SCC mostly occurs following regular exposure to sunlight or other UV radiation. SCC causes extensive destruction of tissue and severe cosmetic deformities. The morbidity and mortality associated with SCC are mostly caused by a subset of high-risk SCC that undergo malignant transformation and metastasize to regional lymph nodes and/or the lungs. Early identification of patients with high-risk SCC is important for the management of these patients.

Cadherins are the major class of cell surface molecules that mediate cell-cell interactions fundamental to the processes of epidermal renewal and homeostasis, and their inappropriate expression or function underlies many diseases of the epidermis.

We investigated the role of T-cadherin in malignant transformation of SCC. Immunohistochemical analysis of skin specimens from patients with SCC showed that loss of T-cadherin is a potential biomarker of malignant and metastatic behaviour of SCC. Gain and loss of function studies *in vitro* using SCC cell cultures showed that loss of T-cadherin expression promotes acquisition of several malignant behavioural traits. Molecular mechanisms underpinning effects of T-cadherin on SCC cell behaviour involve modulation of epidermal growth factor receptor (EGFR) pathway activity. *In vivo* experimental models confirmed that loss of T-cadherin expression in SCC is relevant to tumourigenic, invasive, and/or metastatic potential.

The study identified T-cadherin as a molecule that plays an important role in epidermal integrity and advanced efforts toward early identification of high-risk SCC lesions.

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Rothermundt Christian | **Metformin in castration-resistant prostate cancer: a multicentre phase II trial conducted by the Swiss Group for Clinical Cancer Research (SAKK 08/09)** (KFS 02641-08-2010)

Study aim

The aim of the study was to assess the activity and tolerability of metformin in patients with prostate cancer. The focus in this disease setting is stabilization of the disease and its symptoms. In a subproject metabolic effects of metformin were analysed. Metformin is a biguanide and is being used in the treatment of diabetes. Metformin has an inhibitory effect on cell proliferation, and metformin can potentially revert the negative effects of androgen deprivation therapy in patients with metastatic prostate cancer.

Methods

Patients with metastatic prostate cancer and proven disease progression under at least one hormonal therapy (bilateral orchiectomy or LHRH agonist) and slow disease progression were accepted into the study. Continuation of LHRH agonist therapy was required in non-castrate patients. Primary endpoint was progression-free survival (PFS) at 12 weeks.

Results

Forty-four patients were enrolled between December 2010 and December 2011. In total, 206 cycles of metformin were administered; median 3.5 cycles (range 1–13). Sixteen patients (36.4 %, 95 % CI: 22.4 %–52.2 %) were progression free at week 12. Four patients (9.1 %, 95 % CI: 2.5 %–21.7 %) were progression free at week 24. Median PFS was 2.8 months (range 0.3–12.5).

Recommendation and patient benefit
Metformin has moderate activity in patients with castration-resistant prostate cancer (CRPC) and has only minor toxicities. In the majority of patients prolongation of PSA-DT can be observed. The results relating to the metabolic status are hypothesis generating: metformin had a modest glucose, insulin, and IGF-1 lowering effect after 12 weeks of treatment. Metformin cannot be recommended for routine use in CRPC; however, we are planning further evaluation of metformin in an earlier disease setting.

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Skoda Radek C. | **The pathogenesis of myeloproliferative disorders** (KLS 02398-02-2009)

Myeloproliferative neoplasms (MPN) are blood disorders characterized by increased red blood cells, leukocytes, and platelets. MPN can progress to acute leukaemia. We identified a somatic mutation in the signalling enzyme Janus kinase 2 (JAK2) that is present in three-quarters of MPN patients. This mutation augments the enzymatic activity of JAK2, which increases the sensitivity of blood cells for incoming growth-promoting signals and thereby promotes the evolution of the disease. New drugs have been developed that inhibit this enzymatic activity, and one compound, ruxolitinib, has been approved for clinical use. However, these JAK2-inhibitors only slow down MPN, but cannot cure it.

During this grant period we developed a mouse model for MPN that is driven by the same JAK2 mutation as found in MPN patients. In this preclinical model we can now test combinations of JAK2 inhibitors with other drugs. This allows rapid screening for the most effective combinations, which can be selected for further testing in humans. In addition, we identified a new gene mutation in a familial form of MPN that predisposes to acquiring MPN.

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Zeller Rolf | **Functional analysis of modulators of SHH pathway activity during the formation of medulloblastomas: a mechanistic study with clinical relevance** (OCS 02368-02-2009)

Background
Medulloblastomas (MB) arise during postnatal cerebellar development and are among the most common and aggressive brain tumours in children. The currently best therapy involves resection of the tumour in combination with radiotherapy and chemotherapy; this often results in severe side effects. Using human biopsies, we established that the protease inhibitor SerpinE2/PN-1 is aberrantly expressed in about 90 % of all medulloblastomas. This PN-1 overexpression correlates well with the SHH subtype of MBs and is also detected in the Ptch1 heterozygous mouse model for SHH-mediated medulloblastoma development. Therefore, our analysis aimed at understanding if and when SerpinE2/PN-1 is essential for medulloblastoma development and if this extracellular modulator is a potential target for development of new molecular therapies.

Methods and approach
Our molecular genetic studies were most done using Ptch1 heterozygous mice and complemented by siRNA inhibition experiments in a human MB-cell line (DAOY). Recently, we also developed mouse progenitor cell lines to allow in-depth mechanistic and molecular analysis.

Results and outlook
Genetic reduction of SerpinE2/PN-1 is sufficient to lower the incidence of medulloblastomas in Ptch1 heterozygous mice by more than 50 %. Functional morphological and molecular analysis establishes that inactivation of one PN-1 allele is sufficient to interfere with growth of the tumour. The proliferation of more than half of all preneoplastic lesions arrests at an early stage and is paralleled by loss of typical markers of medulloblastoma growth. These alterations show that PN-1 overexpression is important for the aberrant SHH pathway activity and tumour cell proliferation. In agreement, PN-1 is overexpressed in regions with high cell proliferation in human MB biopsies. Further, siRNA mediated inhibition of PN-1 synthesis in a human MB-cell line significantly reduces cell proliferation. These results indicate that a specific PN-1 inhibitor in combination with SHH inhibitors may lower or even inhibit the growth of medulloblastomas.

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Further completed research project in 2012

Heim Markus Hermann | KLS 02522-02-2010 | CHF 218,300.–
Klinik für Gastroenterologie und Hepatologie, Universitätsspital Basel, Basel
Hepatocarcinogenesis in chronic hepatitis C

List of approved research projects in 2012

Total funds allocated: CHF 4,145,600.–

Ammann Roland A. | KFS 02933-02-2012 | CHF 63,300.–
Abteilung für Hämatologie/Onkologie, Universitätsklinik für Kinderheilkunde, Inselspital, Universitätsspital Bern, Bern
The impact of lowering fever limits on the rate of fever in chemotherapy induced neutropenia (FN): a prospective single-centre observational study in children and adolescents with cancer (Paediatric FN Definition 2012 Bern)

Bach Cuadra Meritxell | KFS 02937-02-2012 | CHF 157,500.–
Département de radiologie, Centre hospitalier universitaire vaudois (CHUV), Université de Lausanne, Lausanne
Towards robust and highly accurate computer assisted treatment planning for intraocular tumours: advanced image processing in a multi-modal framework

Beck Popovic Maja | KFS 02886-02-2012 | CHF 176,800.–
Service et laboratoire d'hématologie, Centre hospitalier universitaire vaudois (CHUV), Lausanne
SPOG-RB-2011: treatment of recurrent or progressive intraocular retinoblastoma. A national phase II study of the Swiss Paediatric Oncology Group

Beerenwinkel Niko | KLS 02892-02-2012 | CHF 263,000.–
Departement Biosysteme, ETH Zürich, Basel
Comparative sequencing of primary renal cell carcinoma: towards a quantitative understanding of tumour diversity and evolution

Bourquin Jean-Pierre | KFS 02920-02-2012 | CHF 248,300.–
Abteilung Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Identification of critical determinants of the microenvironmental support for acute lymphoblastic leukaemia

Brisken Cathrin | KLS 02907-02-2012 | CHF 339,200.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Mechanisms triggering cell proliferation in ER$^+$ breast cancers in novel preclinical models

Citi Sandra | KLS 02878-02-2012 | CHF 201,700.–
Département de biologie cellulaire, Université de Genève, Genève
The role of the new adherens junction protein PLEKHA7 in cancer and signalling

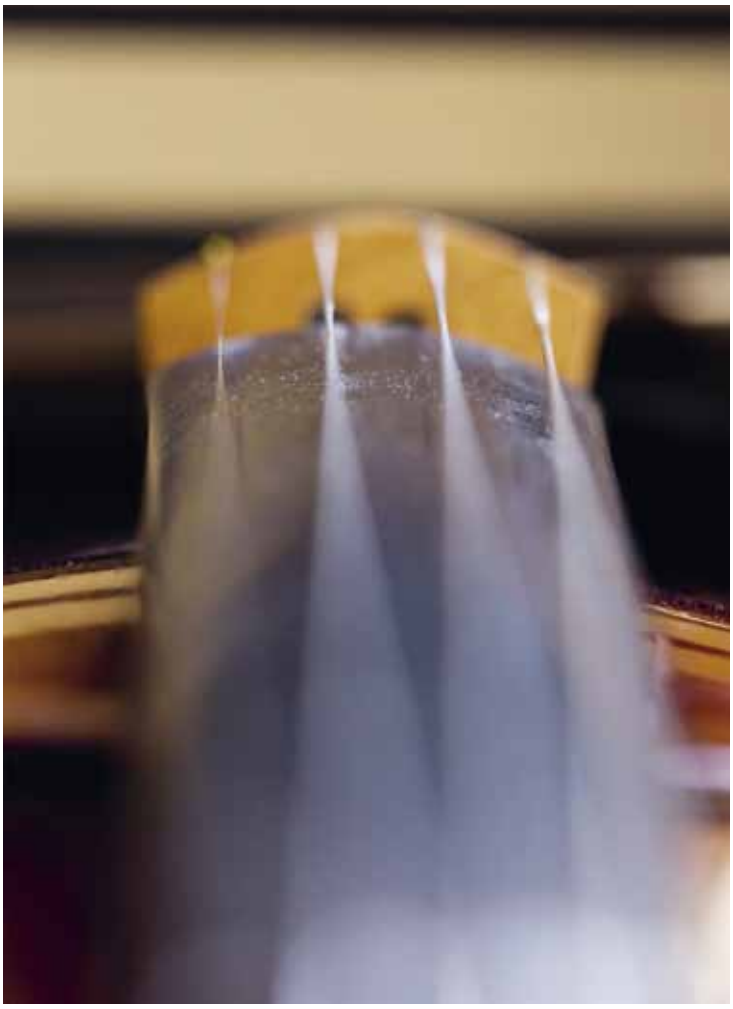
Dotto Gian-Paolo | KLS 02922-02-2012 | CHF 202,500.–
Département de biochimie, Faculté de biologie et de médecine, Université de Lausanne, Epalinges
MicroRNAs as determinants of squamous cell carcinoma development in immune-suppressed patients

Fey Martin F. | KFS 02919-02-2012 | CHF 274,700.–
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
HOVON 102 AML/SAKK 30/09: randomized study with a run-in feasibility phase to assess the added value of clofarabine in combination with standard remission-induction chemotherapy in patients aged 18–65 years with previously untreated acute myeloid leukaemia (AML) or myelodysplasia (MDS)

Gautschi Oliver | KLS 02943-02-2012 | CHF 154,800.–
Medizinische Onkologie, Luzerner Kantonsspital, Luzern
SAKK 19/09: bevacizumab, pemetrexed and cisplatin, or erlotinib and bevacizumab for advanced non-squamous NSCLC stratified by EGFR mutation status. A multicentre phase II trial including biopsy at progression (BIO-PRO trial)

Hegi Monika | KFS 02949-02-2012 | CHF 306,700.–
Laboratoire de biologie et génétique des tumeurs, Service de neurochirurgie, Centre hospitalier universitaire vaudois (CHUV), Lausanne
The methylome of low grade glioma: identification of novel therapeutic targets and biomarkers for response to treatment

Heinzelmann-Schwarz Viola | KFS 03013-08-2012 | CHF 200,600.–
Klinik für Operative Gynäkologie und Gynäkologische Onkologie, Universitätsspital Basel, Basel
Detection of anti-glycan antibodies in ovarian cancer long-term survivors



Michalik Liliane | KFS 02900-02-2012 | CHF 202,500.–
Centre intégratif de génomique (CIG), Université de Lausanne, Lausanne
PPARγ ligands: an emerging therapeutic strategy to treat malignant melanoma

Nikolaev Sergey | KLS 02939-02-2012 | CHF 200,000.–
Département de médecine génétique et de développement, Université de Genève, Genève
Basal cell carcinoma: an integrative approach to detect somatically acquired sequence variants that identify genes involved in carcinogenesis

Rentsch Cyrill A. | KFS 03059-08-2012 | CHF 230,600.–
Urologische Klinik, Universitätsspital Basel, Basel
Identification of genomic correlates of cancer immunoediting in responders and non-responders to Bacillus Calmette-Guérin immunotherapy in bladder cancer

Rimoldi Donata | KFS 03056-08-2012 | CHF 209,900.–
Centre Ludwig de l'Université de Lausanne pour la recherche sur le cancer, Université de Lausanne, Epalinges
Investigating somatic variants in cutaneous melanoma

Romero Pedro | KFS 03064-08-2012 | CHF 204,600.–
Centre Ludwig de l'Université de Lausanne pour la recherche sur le cancer, Université de Lausanne, Epalinges
Dissecting the complexity of antigen-specific CD4 T-cell responses in cancer patients

Soltermann Alex | KFS 02984-08-2012 | CHF 185,800.–
Institut für Klinische Pathologie, Universitätsspital Zürich, Zürich
Desmoplastic stroma of lung squamous cell carcinoma – relevance for targeted therapy and drug resistance

Stern Martin | KFS 03030-08-2012 | CHF 120,600.–
Klinik für Hämatologie, Universitätsspital Basel, Basel
Role of activating killer cell immunoglobulin-like receptors in natural killer cell cytotoxicity against leukaemic cells

Wolfer Anita | KFS 02935-02-2012 | CHF 202,500.–
Centre pluridisciplinaire d'oncologie (CePo), Centre hospitalier universitaire vaudois (CHUV), Lausanne
The role of MYC in cancer cell invasion and metastasis

Approved bursaries in 2012

Total funds allocated: CHF 472,150.–

Böhm Steffen | BIL KLS 02883-02-2012 | CHF 58,400.–
The inflammatory cytokine Interleukin-6 as a therapeutic target in ovarian cancer
Destination: Centre for Cancer & Inflammation, Queen Mary University, London, United Kingdom

Gamondi Claudia | BIL KLS 02942-02-2012 | CHF 38,750.–
Extended visit to the international observatory on end of life care
Destination: Division of Health Research, Faculty of Health & Medicine, Lancaster University, Lancaster, United Kingdom

Hermanns Thomas | BIL KFS 03036-08-2012 | CHF 136,000.–
A non-invasive personalized urinary biomarker panel for the early diagnosis of bladder cancer
Destination: Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Canada

Kollár Attila | BIL KFS 02989-08-2012 | CHF 57,200.–
Translational study of pre-operative pazopanib in patients with resectable soft tissue sarcomas
Destination: Institute of Cancer Research, Royal Marsden Hospital, Sutton, United Kingdom

Meyer Sara Christina | BIL KFS 03005-08-2012 | CHF 47,100.–
Genetic and functional insights into the pathogenesis of myeloproliferative neoplasms
Destination: Memorial Sloan-Kettering Cancer Center, New York, USA

Morand Grégoire | BIL KFS 03002-08-2012 | CHF 41,400.–
Clinicopathological implications of EMT relevant genes in oral cancer
Destination: Segal Cancer Center, Jewish General Hospital, McGill University, Montreal, Canada

Volorio Angela | BIL KFS 02995-08-2012 | CHF 93,300.–
Transcriptomic-, proteomic-, and genomic-based prognostic and treatment-predictive biomarker discovery in the TEACH clinical trial
Destination: Center for Cancer Research, Harvard Medical School, Massachusetts General Hospital, Charlestown, USA

Presentation of approved research projects in 2012

Ammann Roland A. | **The impact of lowering fever limits on the rate of fever in chemotherapy induced neutropenia (FN): a prospective single-centre observational study in children and adolescents with cancer (Paediatric FN Definition 2012 Bern)**
(KFS 02933-02-2012)
Duration: 01.07.2012 – 31.12.2013

Fever in neutropenia (FN) (deficiency of white blood cells) is the most frequent potentially lethal side effect of chemotherapy for cancer. Thanks to emergency hospitalization and immediate start of intravenous broad-band antibiotics, today less than 1% of children with FN die. But bacterial infections are detected in only one-quarter of FN. Thus, three-quarters of FN are overtreated, implying – strictly speaking – unnecessary hospitalizations, antibiotics, and high costs. One way to reduce this overtreatment is to restrict making the diagnosis of FN by increasing the fever limit applied.

This limit currently varies in paediatric oncology from 37.5 °C to 39.0 °C. For higher fever limits, both the efficacy (reduction of the number of FN diagnoses made) and the safety (risk of complications because of delayed diagnosis and start of therapy) are not known. In Bern, the highest fever limit of ≥ 39.0 °C is used. This allows us to study the influence of hypothetically lowering the fever limit on the frequency of FN diagnoses, without changing diagnosis and therapy of FN in reality. This purely observational study can thus assess the efficacy of a higher fever limit. The results will also allow us to refine the design of a future interventional study assessing also the safety of a high fever limit.

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Bach Cuadra Meritxell | **Towards robust and highly accurate computer assisted treatment planning for intraocular tumours: advanced image processing in a multi-modal framework** (KFS 02937-02-2012)
Duration: 01.01.2013 – 31.12.2015

The eye is one of the most important sensory organs. Undesirable side effects or failure of radiotherapy treatments of ocular tumours could be fatal for the vision of the patient and consequently lead to life-threatening situations. Treatment planning for the eye needs to be very precise to accurately target the tumour while preserving surrounding healthy tissues (to prevent the development of secondary tumours). Nowadays, treatment planning is done based on different medical imaging methods such as computed tomography, fundus photography, ultrasound, or magnetic resonance imaging. However, these images are observed independently of each other and are combined mentally by the radiation oncologists to obtain an overall vision of the tumour and its location.

In this project, advanced image processing algorithms will help to produce a comprehensive and objective picture of the tumour and its surrounding healthy tissues. We will develop a virtual eye model that will be adapted to the different imaging modalities and thus to the patient anatomy. This patient-specific eye model will allow all existing image modalities to be efficiently fused, will help to plan the therapy in a reproducible manner, and will allow calculation of the exact position of the eye relative to the treatment unit.

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Beerenwinkel Niko | **Comparative sequencing of primary renal cell carcinoma: towards a quantitative understanding of tumour diversity and evolution**
(KLS 02892-02-2012)
Duration: 01.07.2012 – 30.06.2014

Carcinogenesis is a dynamic process characterized by tumour growth and the accumulation of mutations in the tumour cell population. Tumour progression is a somatic evolutionary process that can be modelled by evolutionary theory. The genetic diversity of tumours is extremely high, both among histologically identical tumours from different patients and within single tumours. The latter intra-tumour genetic diversity is largely responsible for drug resistance development. We analyse genomic variation in renal cell carcinoma using modern high-throughput sequencing technology. Our goal is to identify the mutations responsible for the progression of the primary tumour and the formation of metastases. We will sequence the cancer genomes of tumour biopsies and analyse the resulting huge amounts of DNA data using specific statistical and bioinformatics methods. The results of these investigations will allow derivation of a quantitative description of tumour evolution and a predictive model of cancer development. These insights on the diversity and progression dynamics of tumours will provide the basis for improved tumour diagnostics and (eventually) treatment.

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Bourquin Jean-Pierre | **Identification of critical determinants of the microenvironmental support for acute lymphoblastic leukaemia** (KFS 02920-02-2012)
Duration: 01.01.2013 – 31.12.2014

Despite impressive progress in the treatment of patients with acute lymphoblastic leukaemia over the last decades, many relapses occur. For these, new treatment approaches are needed. Leukaemia cells are critically dependent upon interactions with the microenvironment in the bone marrow, which may provide new opportunities for therapeutic intervention. In the bone marrow, acute lymphoblastic leukaemia (ALL) cells were shown to displace normal haematopoietic stem cells (HSC) from their niche, indicating that similar components constitute a niche for both normal and leukaemia stem cells. Given the diversity of genetic lesions in ALL and based on preliminary data, we postulate that different patterns of interactions between ALL cells exist that may have therapeutic implications. Here we propose to take advantage of an *in vitro* co-culture model of human primary ALL cells with bone marrow stromal cells to identify interactions that are critical for leukaemia survival and to determine common and distinct features for the protection of ALL selected from genetically and clinically distinct ALL subgroups.

In serum-free conditions most primary leukaemia cells can be maintained on hTERT-immortalized mesenchymal stromal cells (MSC) *in vitro*. In contrast, in most cases these xenografts do not survive longer than one week in cell suspension cultures. This constituted the basis for a focused candidate gene siRNA approach using our newly established automated microscopy-based platform. Among 100 genes that were selected based on their expression on MSC, the existence of predicted interaction partners on ALL cells, and/or reported experimental evidence for a haematopoietic niche function in other models, we identified 16 genes that contribute to ALL cell survival. Here we propose to further characterize these candidates functionally. It will be important to evaluate if given signals are important only for a subset of cases or if it will be possible to identify general survival mechanisms. To investigate these protective signals *in vivo*, we will develop an animal model of the leukaemia niche. We expect to identify important signals from the bone marrow microenvironment that support leukaemia survival; this will lead to a better understanding of critical interactions between leukaemia cells and their microenvironment.

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Brisken Cathrin | **Mechanisms triggering cell proliferation in ER⁺ breast cancers in novel preclinical models** (KLS 02907-02-2012)
Duration: 01.09.2012 – 31.08.2015

Two-thirds of breast cancers are oestrogen receptor positive (ER⁺). The 5-year survival rate of patients with ER⁺ tumours is better than that of patients with oestrogen receptor-negative tumours, but one-third of ER⁺ tumours become resistant to hormonal therapies and some will recur decades later. We still do not understand this behaviour and lack models that allow us to study this *in vivo*. We are developing novel models that mimic the human situation more closely and bear more clinical relevance. Specifically, we inject human ER⁺ breast cancer cells through the nipple into the mouse milk duct system. The injected cells give rise to lesions that resemble human *in situ* carcinomas and progress to invasive disease.

With this approach, we will study how oestrogen makes tumours grow. We propose that oestrogen tells ER⁺ tumour cells to make and secrete various factors that stimulate the neighbouring cells. Such secreted factors are excellent targets for promising new drugs, humanized antibodies. For one of the factors we are studying, RANKL, such antibodies (denosumab) are already used in patients with bone disorders. Our work will help determine whether breast cancer patients might benefit from this drug and whether other factors should be targeted. The ability to interfere with what happens downstream of the activation of ER may benefit patients whose tumours have become resistant to hormonal therapy.

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Citi Sandra | **The role of the new adherens junction protein PLEKHA7 in cancer and signalling** (KLS 02878-02-2012)
Duration: 01.07.2012 – 30.06.2015

The majority of cancers derive from epithelial cells, which cover body cavities and surfaces and form glands. In cancer, cells can lose their ability to adhere well to each other and acquire the ability to migrate and move within the body, which can lead to the formation of metastases. Specialized structures called “adherens junctions” control the adhesion between epithelial cells and are also implicated in the regulation of cell proliferation and migration. We are studying a new protein of adherens junctions, PLEKHA7, which links these junctions to the cytoskeleton. The objective of our research is to understand how PLEKHA7 is implicated in the regulation of adhesion, proliferation, migration, and signalling pathways.

We will study the expression of PLEKHA7 in human cancer, and we will artificially modify its expression levels in cultured cells to study the consequences of either the loss or overexpression of PLEKHA7 on proliferation, migration, gene expression, and epithelial barrier. This research project is particularly innovative, since PLEKHA7 was discovered very recently, and it will allow us to advance our knowledge about the cellular mechanisms underlying epithelial cancers.

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Dotto Gian-Paolo | **MicroRNAs as determinants of squamous cell carcinoma development in immune-suppressed patients** (KLS 02922-02-2012)
Duration: 01.10.2012 – 30.09.2015

Skin cancer is frequent in the general population. Some groups are known for their even higher risk of this common cancer. Organ transplant recipients nowadays live a long time with a donated organ such as heart, liver, or kidney. This success does not come without a cost, however, and relies on life-long immunosuppression through a combination of drugs. An important problem related to chronic immunosuppression is the increased occurrence of cancer at large and in particular, at the top of the list, of squamous cell carcinoma of the skin. We have improved our understanding of why this cancer in particular increases by an impressive 60- to 100-fold compared to the general population. Apparently, the immunosuppressive drugs also exert a direct effect on skin cells, resulting in increased formation of squamous cell carcinoma of the skin. Many questions remain unanswered, though. One of these open questions concerns the importance of microRNAs in the disease development. MicroRNAs are a newly described class of nucleotides that modulate protein expression and thus behaviour in many conditions in particular in cancer.

Recently, we found a limited number of microRNAs to be distinctly changed in squamous cell carcinoma of the skin, which may be of particular importance in the development of squamous cell carcinoma in organ transplant recipients. We aim to unravel the role of these microRNAs in more detail. Functional assays have already shown an impact of manipulation of these microRNAs *in vitro*, where we observed changes in proliferation, invasion, and migration. We have started to delve into intracellular signalling pathways to understand how these microRNAs mediate their effect on the cellular level. Based on the expected findings, we hope to learn about the potential to manipulate microRNAs in skin with the aim to develop new therapeutic interventions.

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Fey Martin F. | **HOVON 102 AML/SAKK 30/09: randomized study with a run-in feasibility phase to assess the added value of clofarabine in combination with standard remission-induction chemotherapy in patients aged 18–65 years with previously untreated acute myeloid leukaemia (AML) or myelodysplasia (MDS)** (KFS 02919-02-2012)
Duration: 01.02.2012 – 31.01.2014

Leukaemia (cancer of the white blood cells) is a severe disorder that, however, can be successfully treated. This clinical trial aims at improving leukaemia chemotherapy through the addition of clofarabine, a new drug, to standard chemotherapy. Patients in Switzerland and the Netherlands are being accrued into this international trial, with 176 patients registered in Switzerland since September 2010. The protocol aims to prove whether the addition of clofarabine to chemotherapy will improve disease-free survival and clearance of leukaemic cells from the bone marrow. The protocol was approved by the respective ethical committees. Funding is necessary for data management and the study coordinator centre to ensure ongoing quality of research. In Switzerland, Prof. Thomas Pabst, MD, senior physician medical oncology, is the responsible trial coordinator (thomas.pabst@insel.ch).

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Hegi Monika | **The methylome of low grade glioma: identification of novel therapeutic targets and biomarkers for response to treatment** (KFS 02949-02-2012)
Duration: 01.08.2012 – 31.07.2015

The treatment of low grade gliomas, a rare type of brain tumour that affects young adults, is difficult. Due to the invasive behaviour of these tumours, complete surgical resection is impossible, and tumours eventually recur within a few years. New insights suggest that epigenetic alterations are the major driver of this tumour type. Epigenetic alterations do not affect the sequence of the DNA bricks but involve modification of the DNA through the addition of methyl groups, which leads to deregulation of the affected genes.

The goal of this project is to analyse these tumour-specific alterations of DNA methylation – the low grade glioma "methylome" – in order to identify new targets for therapy. The idea is that some of these epigenetic alterations can be converted into the "Achilles heel" of the affected tumours upon treatment with certain classes of anti-cancer agents. The methylome of a series of low grade gliomas from patients treated homogenously within a large international clinical trial is being analysed genome-wide. Correlation of epigenetic alterations with clinical data, such as benefit from therapy, should allow identification of particularly cancer-relevant alterations that might be therapeutically targetable.

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Heinzelmann-Schwarz Viola | **Detection of anti-glycan antibodies in ovarian cancer long-term survivors**
(KFS 03013-08-2012)
Duration: 01.02.2013 – 31.01.2016

With a 5-year survival rate of only 20 %, ovarian cancer has the highest mortality rate within all gynaecological cancers. This rate is domineered by a highly aggressive type of serous ovarian cancers that commonly present with chemotherapy resistance. We have previously identified antibodies in the blood of 250 Swiss ovarian tumour patients who were long-term survivors using a new array technology. In this project we will validate these findings in a much larger Australian cohort of 100 long-term survivors using various validation methods. We will also investigate the functional role of the identified antibodies.

Project coordinator
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Michalik Liliane | **PPARγ ligands: an emerging therapeutic strategy to treat malignant melanoma**
(KFS 02900-02-2012)
Duration: 01.01.2013 – 31.12.2015

Malignant melanoma remains an incurable and aggressive form of cancer, despite recent major clinical breakthroughs. Not all patients benefit from recent treatments, and tumours finally acquire resistance to treatment, severely limiting its efficacy. Therefore, malignant melanoma remains a medical challenge, and further investigation is urgently necessary to discover alternative or adjuvant therapeutic strategies. Recent research developments strongly suggest that the efficacy of the treatments will improve with a better diagnosis of the tumours followed by the rational use of a variety of therapeutic targets and personalized treatment. In these respects, peroxisome proliferator-activated receptor gamma (PPARγ) as a therapeutic target or diagnosis marker certainly deserves attention and requires additional research. Combined therapies targeting PPARγ with existing treatments would offer the opportunity to keep each drug at lower doses and to increase the chance of a therapeutic response.

We propose to undertake a study to understand PPARγ's potential as a therapeutic target in melanoma by integrating experimental and clinical data. We believe that the data collected in this project will benefit the clinic by investigating novel strategies of medical intervention to improve melanoma diagnosis and treatment.

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Nikolaev Sergey | **Basal cell carcinoma: an integrative approach to detect somatically acquired sequence variants that identify genes involved in carcinogenesis**
(KLS 02939-02-2012)
Duration: 01.07.2012 – 28.02.2015

Basal cell carcinoma (BCC) is the malignant skin tumour induced primarily by exposure to sunlight. Its frequency has increased significantly in all European countries and North America (1.6 million cases in 2006), making it the leading cause of cancer in humans. Knowledge of the genetic mechanisms underlying the development of malignancy has become the priority for targeted therapies. In recent years the search for specific mutations in tumour DNA has been performed genome-wide. This allows a catalogue of mutations present in the affected tissue to be established and genes critical for tumour development to be identified.

The aim of the project is to determine the mutational profile of BCCs. In collaboration with the University of Lausanne and the Ludwig Institute, the University of Geneva (Department of Medical Genetics) recently identified mutations important in the development of another skin cancer, melanoma. This therefore suggests the efficiency of the genomic analysis applied for the study of BCCs. Within three years, we plan to collect hundreds of basal cell carcinomas and analyse their DNA. The precise role of detected genes in cancerogenesis will be established through functional assays. Our results will provide a better understanding of how to prevent the skin cancers and will open up avenues for novel therapeutic approaches.

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Rentsch Cyrill A. | **Identification of genomic correlates of cancer immunoediting in responders and non-responders to Bacillus Calmette-Guérin immunotherapy in bladder cancer** (KFS 03059-08-2012)
Duration: 01.11.2012 – 31.10.2015

We are interested in how cancer escapes the control of the immune system; specifically, we would like to understand the genetic changes of a recurrent tumour after immunotherapy in comparison to the tumour before immunotherapy. The high recurrence rate of bladder cancer, the easy access to tumours, and the clinically established highly effective immunotherapy in combination with state-of-the-art genetic analysis will allow us to investigate the genetic changes in recurrent cancer after immunotherapy. The definition of genetic changes associated with cancer immune escape will have implications for the field of cancer immunotherapy in general and will influence the selection of patients undergoing immunotherapy for bladder cancer.

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Rimoldi Donata | **Investigating somatic variants in cutaneous melanoma** (KFS 03056-08-2012)
Duration: 01.04.2012 – 31.03.2014

Ten years ago, genomic studies identified a mutation in a gene called BRAF in half of cutaneous melanoma, the most malignant skin tumour that is responsible for 1.7 % of cancer deaths in Switzerland. The mutated BRAF protein produced by melanoma cells causes an overactivation of a cellular signalling pathway called MAPK, thus leading to uncontrolled cell growth. This key discovery led to the development of a specific anti-BRAF treatment that has entered the clinic. New DNA sequencing technologies (next generation sequencing) now allow us to view the entire catalogue of mutations in the DNA of cancer cells. By applying these technologies, we recently identified novel mutations that may play a role in malignant melanoma. In particular, we found mutations in a gene called MEK, which is also a component of the MAPK pathway.

One major goal of this study is to understand if and how the "hyperactive" MEK proteins that result from these mutations contribute to melanoma development and influence the response to anti-BRAF treatments. To this end, we will use melanoma cells manipulated in the laboratory and in which we can modulate the production of the mutant MEK proteins. We hope with this project to reach a better understanding of the role of the different somatic mutations affecting the MAPK pathway in melanoma.

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Romero Pedro | **Dissecting the complexity of antigen-specific CD4 T-cell responses in cancer patients**
(KFS 03064-08-2012)
Duration: 03. 02. 2013 – 02. 02. 2016

We propose to carry out an in-depth analysis of the tumour antigen-specific CD4 T-cell responses that take place in patients with metastatic melanoma, an aggressive tumour of the skin that is on the rise in developed countries and for which there are precious few therapeutic options of limited efficacy. CD4 T-cells have the potential to orchestrate the anti-tumour immune responses and are essential for efficient immune attack of tumour cells. In this project, we will first analyse the CD4 T-cell responses induced in patients with growing tumours. More concretely, we aim to characterize CD4 T-cells specific for tumour antigens and evaluate the effect of anti-tumour immunotherapies on these cell subsets. To do this, we will adapt recent technical advances in the field, which include the so called T-cell libraries using CD4 T-cells purified from patients' peripheral blood, fluorescent MHC class II/peptide multimers for the direct identification and isolation of tumour antigen-specific CD4 T-cells, and single cell PCR. The last technique allows us to learn about specific gene expression from single isolated T-cells.

We will then study cohorts of patients immunized with therapeutic cancer vaccines. Through this, we can obtain a complete description of the CD4 T-cell responses against certain tumour antigens as they occur during tumour progression and as they are modified by specific vaccination. The descriptors will include the determination of the quantity of each specific T-cell, their functional competence and particularly their ability to recognize tumours and to orchestrate anti-tumour immune responses, the modulation of both parameters by vaccines, and their geographical distribution in the tumour-bearing patient.

The results of this research study will greatly help advance our understanding of the interactions between the adaptive immune system and cancer. In turn, this knowledge will greatly help to improve current candidates for therapeutic vaccination. The field of tumour immunology and cancer immunotherapy has advanced to a point where cancer vaccines can become novel components of the therapeutic approaches in the clinic. Therefore, this project should contribute towards more and better cancer vaccines for the treatment of cancer patients.

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Soltermann Alex | **Desmoplastic stroma of lung squamous cell carcinoma: relevance for targeted therapy and drug resistance** (KFS 02984-08-2012)
Duration: 01. 02. 2013 – 31. 01. 2016

Lung squamous cell carcinoma (SCC) elaborates a prominent desmoplastic stroma. SCC cells infiltrate into this stroma as small cohorts or sheets and display epithelial-mesenchymal transition (EMT) at the invasion front. Thereby, cells acquire a fibroblastoid, motile phenotype, upregulate EMT proteins such as periostin and L1CAM, and downregulate the cell adhesion molecule E-cadherin. We detected periostin in lung cancer pleural effusions by mass spectrometry and found it to be a non-small cell lung carcinoma (NSCLC) prognosticator.

Here we aim to perform a quantitative and qualitative analysis of the lung SCC stroma. We will compare chemotherapy-naïve versus treated and pT1 versus pT3 tumours in order to assess the prognostic impact of stromal features and to define the topographic region with the highest drug resistance. The tumour-stroma ratio will be morphometrically measured, using cytokeratin immunohistochemistry (IHC) on both tissue microarray (TMA) cores and whole sections, following analysis by the C-Path algorithm. Lung SCC will be compared with head and neck SCC. Architectural parameters will be correlated with next generation sequencing data, including oncogenic alterations such as discoidin domain receptor 2 (DDR2) mutations. Expression of EMT proteins at the invasion front will be assessed by micro-IHC, using the microfluidic probe technology (IBM Research).

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Stern Martin | **Role of activating killer cell immunoglobulin-like receptors in natural killer cell cytotoxicity against leukaemic cells** (KFS 03030-08-2012)
Duration: 02. 01. 2013 – 01. 01. 2015

The standard treatment of patients with acute leukaemia consists of intensive chemotherapy followed by stem cell transplantation. Due to the growth of unrelated donor registries, more than one compatible donor is frequently identified for a patient. Research in recent years has investigated whether further genetic testing allows selection of an optimal donor. In particular, genetic polymorphisms associated with a reduced rate of disease relapse are of interest.

As a part of these efforts, genes coding for the killer cell immunoglobulin-like receptors (KIRs) have been identified as playing a role in the prevention of disease relapse after transplantation. KIRs are primarily expressed on a subset of white blood cells termed natural killer (NK) cells and can be divided into two groups, with either an activating or inhibitory function. Epidemiological research has shown that

the more genes for activating receptors the donor carries, the smaller the relapse risk is. Accordingly, studies are currently running to determine whether preferential selection of donors with a large number of activating KIRs receptor genes improves the outcome of transplantation. The biological mechanism involved in this protection is so far unclear. It seems plausible that activating KIRs recognize molecules expressed on leukaemia cells. As a part of the current research projects, we will produce synthetic KIRs and study their binding to leukaemia cells.

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Wolfer Anita | **The role of MYC in cancer cell invasion and metastasis** (KFS 02935-02-2012)
Duration: 01.07.2012 – 30.06.2015

Cancer is one of the leading causes of death worldwide, and metastasis is the primary cause of death in cancer patients. A more detailed understanding of the mechanisms of the metastatic process will allow the development of targeted therapeutic approaches to prevent the dissemination of tumour cells. In addition, molecules involved in the metastatic process might also serve as prognostic markers, guiding treatment decisions using the currently available therapeutic agents. In previous work, I have shown that 13 gene expression signatures prognostic of poor outcome are coordinately regulated by MYC. A core interactome of 20 genes contained in these 13 gene expression signatures was coordinately regulated by various oncogenic stimuli and was centred on MYC. The loss of MYC in a metastatic xenograft mouse model led to a significant decrease in lung metastases. Here I propose to study the role of the 20 gene interactome in the development of distant metastases using gain and loss of function studies in human breast cancer cell lines and mouse xenograft models. Given that these gene expression signatures, the analysis of which led to the identification of MYC as a regulator of tumour invasion, are of prognostic value in actual human tumours, it seems highly likely that any findings of further downstream mechanisms will be of clinical importance.

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Further approved research projects in 2012

Beck Popovic Maja | KFS 02886-02-2012 | CHF 176,800.–
Service et laboratoire d'hématologie, Centre hospitalier universitaire vaudois (CHUV), Lausanne
SPOG-RB-2011: treatment of recurrent or progressive intraocular retinoblastoma. A national phase II study of the Swiss Paediatric Oncology Group

Gautschi Oliver | KLS 02943-02-2012 | CHF 154,800.–
Medizinische Onkologie, Luzerner Kantonsspital, Luzern
SAKK 19/09: bevacizumab, pemetrexed and cisplatin, or erlotinib and bevacizumab for advanced non-squamous NSCLC stratified by EGFR mutation status. A multicentre phase II trial including biopsy at progression (BIO-PRO trial)

Putting psycho-oncological research findings into clinical practice

The topics in psycho-oncological research start out from two different perspectives: investigation of the psychological and social consequences of cancer for persons with cancer and their family members, and study of possible effects of psychological and social factors on the development and course of cancer. Psycho-oncological research is thus a very broad field, ranging from early detection to care for the dying and support to the bereaved. The benefit of this research for the care of persons with cancer and their families is uncontested. The benefit for health care professionals in medicine and nursing is less obvious. The answer to the question as to the extent to which psycho-oncological findings are put into clinical practice differs depending on the research topic.

Quality of life as a central concern

A central concern of psycho-oncological research is to improve or at least maintain the quality of life of persons with cancer and their families. Prior to the development of this research, mainly psychiatric criteria were used to indicate the need for psychosocial intervention or psychotherapy. During the course of cancer, 25 to 35 per cent of patients show classifiable psychiatric disorders, whereby the percentage varies strongly with diagnosis, cancer stage, and psychiatric assessment method. But questions about dealing with limitations and stresses caused by cancer and cancer treatment are much more complex and more subtle than can be assessed using psychiatric criteria alone. For example, facing existential questions and questions concerning biographical topics is a frequent reason for people to seek psycho-oncological support.

Prof. Jürg Bernhard, PhD
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Within psycho-oncological research, persons with cancer assess aspects of their quality of life from their own point of view and report their personal experiences. This approach has produced a crucial finding: Patients' "subjective" experience of the stresses caused by cancer and cancer treatment often do not match the perceptions of the health care professionals. For instance, among patients with breast cancer, neuropsychological tests can demonstrate cognitive limitations such as memory problems caused by chemotherapy and hormone therapy, sometimes also years later.[1] But when the breast cancer survivors are asked to rate their cognitive dysfunction on a scale, there is often no correlation or only a low correlation with the "objective" test results.[2] This inconsistency is caused, among other things, by emotional stress.

When values shift

These ratings by the patients may be unexpected, but they do not call into question the validity of self-assessment by patients. Instead, the findings lead us to new questions and areas of study. During the course of the disease, it is enormously demanding for persons with cancer to have to adapt the handling of their everyday lives to the new conditions, such as making adjustments due to physical weakness. Having to make these adjustments leads to a shift in their perceptions, as their perception of "good" well-being comes to differ more and more from the notions of well-being of healthy persons. This shift in the individual standard (for example, regarding sensation of pain) and personal needs and preferences can make the limitations and stresses caused by cancer more bearable. This process is impressively documented in patients' self-reports of their experience. If those treating the patient could communicate the prospect of this shift in values, it could mean a lot for patients, especially during a stressful treatment or if the cancer progresses.

Attentiveness to personal experience also leads to increased sensitivity for changes in one's body and thus for the underlying disease process. Studies have shown that patients' self-rating of aspects of quality of life, especially physical well-being, is one of the best prognostic indicators in many advanced stage cancers – also in statistical comparison with known biomedical prognostic factors.[3] This finding confirms the validity of self-assessment and importance of a person's own perceptions for decision making, such as the decision to continue or discontinue treatment when cancer develops to an advanced stage.

Psycho-oncological interventions with patients

Very important for clinical practice is that aspects of quality of life should not only be captured in research studies; the findings and their consequences should also inform treatment and care. There are basically two complementary types of psycho-oncological interventions. In direct contact with patients and their families, there are assessments and counselling, short and often behaviour-oriented interventions and also longer-term support and psychotherapy that focus on dealing with the illness and controlling symptoms (such as dealing with uncertainty). Interventions for professionals in medicine, nursing, social work, and other areas include supervision and further and continued education and training focusing on communication (for example, communicating bad news) and conveying psycho-oncological information.

The effect of many psycho-oncological interventions in direct contact with persons with cancer and their families is very well documented, especially with regard to reducing anxiety and depression.[4,5] In studies, the treatment results vary greatly: Treatment success is considerably dependent upon whether the intervention is adjusted to the intensity of the patient's distress. The psycho-oncological treatments are generally much more effective with patients with high levels of distress than with patients with low levels.[5] This finding is plausible not only clinically. It also confirms the experience that individualized patient care is imperative, even with interventions that are standardized and integrated in the oncological care. Varying treatment effectiveness of psycho-oncological interventions is also found for different cancers and stages of cancer, but these differences have only begun to be studied.

In recent years, the "classical" psycho-oncological question regarding risk factors for morbidity and mortality has been relativized. Newer psycho-oncological studies investigating the effect of psycho-oncological treatment on the course of the cancer have found that intervention improves well-being and quality of life but has no effect on survival. These findings, too, are important for clinical practice, since they help therapists to convey a clear orientation to patients and to put empirically disproved but popular notions into appropriate perspective. For example, the frequent assumption by persons with cancer, "I must not feel sad, because that will have a negative effect on my immune system and thus make it harder to fight the cancer", is not scientifically tenable. Due to the methodological complexity of these issues, bio-psycho-social interactions are no longer studied today in an overall way but instead more with regard to specific factors, such as disturbance of the circadian rhythm (our "inner clock") as a consequence of stress.

Psycho-oncological interventions with health care professionals

Psycho-oncological offerings for professionals in medicine and nursing consist mainly in courses on communicating with patients. The effect of communication skills training on health care professionals has been studied less than the effect of interventions on persons with cancer. But there is documented evidence concerning important aspects,[6,7] first and foremost on training patient-centred behaviour, such as training physicians to address emotions. This behaviour can be put into clinical practice comparatively easily and helps to ease patients' burden. Interventions with health care professionals can also have a positive effect on patients' psychosocial adaptation. For example, good preparation for invasive surgery results in less emotional distress and better psychosocial and in part also physical rehabilitation. It is not yet clear how communication skills training can change the behaviour of health care professionals not only in the short and medium term but also long-term.

Integrative understanding of illness

The need for treatment and care that is comprehensive also in the psychosocial sense must no longer be made dependent upon general evidence of the effectiveness of psycho-oncological interventions. Important for clinical practice is differentiated assessment of the needs of persons with cancer. In addition, psycho-oncological services have to keep up with developments in oncology. Psycho-oncological guidelines, which are being developed in Switzerland and in many other countries, are an important step in integrating these services into oncological care.[8] Consequently, there should be a greater emphasis on health services research in this area in the coming years.

The question regarding "subjective" tolerance and support measures often arises also with the new and often complex treatment planning. With the additional treatment possibilities for advanced stage cancer, decision making and communication become more difficult for both the persons with cancer and healthcare professionals. For these issues, too, a comprehensive understanding of illness and thus an integrated approach is the way towards clinically relevant results.

Prof. Jürg Bernhard, PhD
Jürg Bernhard studied clinical psychology and psychopathology at the University of Zurich and completed training in psychotherapy. Bernhard trained as a psycho-oncologist at Memorial Sloan-Kettering Cancer Center in New York. He is assistant professor of psychosocial medicine and psycho-oncology at the Medical Faculty of the University of Bern. He heads the Psycho-Oncology Service in the Department of Medical Oncology at Inselspital, Bern University Hospital. In addition to his clinical work he also works in psycho-oncological research, currently focusing on the effects of cancer treatment on quality of life and cognitive functioning, and decision making in physician/patient communication. He also works for psycho-oncology in the framework of the National Cancer Programme 2011–2015.
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List of completed research projects in 2012

Bernhard Jürg | OCS 02232-04-2008 | CHF 158,600.–
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
Erythropoiesis-stimulating factors and quality of life in cancer patients: individual patient data meta-analysis based on randomized controlled trials

Kiss Alexander | OCS 02400-02-2009 | CHF 187,200.–
Abteilung für Psychosomatik, Departement Innere Medizin, Universitätsspital Basel, Basel
A cognitive-behavioural mindfulness intervention to improve health-related quality of life, depression and fatigue among long-term haematopoietic stem cell transplant survivors

Lehr Hans-Anton | KFS 02775-02-2011 | CHF 79,000.–
Institut universitaire de pathologie de Lausanne (IUP), Centre hospitalier universitaire vaudois (CHUV), Lausanne
Biomedical research on human tissues: in the twilight zone between autonomy and data protection. What do health professionals, patients and lay persons think about issues of consent and transparency in medical research, teaching, and quality control?

Mueller Michael D. | KFS 02456-08-2009 | CHF 116,500.–
Gynäkologie und Gynäkologische Onkologie, Universitätsklinik für Frauenheilkunde, Inselspital, Universitätsspital Bern, Bern
Creating and validating a patient-pertinent instrument to assess symptoms experienced related to surgical wounds in women with vulvar neoplasms – a mixed methods study (WOMAN-PRO)

Tschudin Sibil | KLS 02577-02-2010 | CHF 62,800.–
Gynäkologische Sozialmedizin und Psychosomatik, Frauenklinik, Universitätsspital Basel, Basel
Fertility preservation in young female cancer patients – assessment of needs regarding decision-making and development of a decision-aid

Presentation of completed research projects in 2012

Bernhard Jürg | **Erythropoiesis-stimulating agents and quality of life in cancer patients: individual patient data meta-analysis based on randomized controlled trials** (OCS 02232-04-2008)

Erythropoiesis-stimulating agents (ESAs) reduce the need for red blood cell transfusions and may improve quality of life in cancer patients. However, they increase the risk of thromboembolic events and mortality during the active study phase, and there is some evidence that they shorten overall survival. We aimed to evaluate and quantify the effects of ESAs on quality of life in cancer by an individual patient data meta-analysis. Previous meta-analyses demonstrated that ESAs effectively reduce fatigue-related symptoms in cancer patients. However, these meta-analyses were based on fewer clinical trials, restricted to the published literature, and might be compromised by publication and reporting biases.

Methods
We included randomized controlled trials studying the effects of ESAs on quality of life in cancer patients. Studies were identified by searching electronic data bases up to January 2011. We conducted meta-analyses on fatigue- and anaemia-related symptoms, as reported by patients using the FACT-Fatigue (FACT-F) and FACT-Anaemia (FACT-An) subscales (primary outcomes), or other validated scales. We did not get permission to use individual patient data. Instead, we analysed the data on group level. We included published and unpublished data from clinical study reports.

Results
We included 37 trials with 10,581 randomized patients. For FACT-F (23 studies, n = 6,108) the effect of ESAs was statistically significant but below the threshold for a clinically important difference. Results for FACT-An (14 studies, n = 2,765) showed ESAs had a positive, statistically significant effect on anaemia-related symptoms that was clinically relevant. We noted selective reporting for FACT-An outcomes: Compared to published data, unpublished data stemming from clinical study reports showed on average smaller treatment effects. In patients receiving chemotherapy, the differences by ESAs were below the threshold for FACT-F and above for FACT-An (both statistically significant).

Conclusions
In cancer patients, particularly patients receiving chemotherapy, we found that ESAs provide a small but clinically important improvement in anaemia-related symptoms. For fatigue-related symptoms, the overall effect did not reach the threshold for clinically important difference. In patients treated with a curative approach it is unlikely that the observed benefits will outweigh the negative effects of ESAs on short-term mortality and thromboembolic events.

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Kiss Alexander | **A cognitive-behavioural mindfulness intervention to improve health-related quality of life, depression, and fatigue among long-term haematopoietic stem cell transplant survivors**
(OCS 02400-02-2009)

Mindfulness-based intervention (MBI) is a group programme aimed at improving dimensions of well-being for patients with a broad spectrum of chronic disorders. This preliminary study examined whether MBI is a feasible and effective intervention for haematopoietic stem cell transplantation (HSCT) survivors of 6 months or longer in terms of enhancing different dimensions of health-related quality of life (HRQoL) (e. g. psychological functioning, positive emotions, social contact, and ability to enjoy life) and decreasing depression, fatigue, and anxiety. In a patient preference trial carried out with 65 patients, patients received their preferred choice of either the experimental intervention MBI or augmented optimal medical care (AOMC) as the control comparison. Patients without clear preference were randomly assigned to one of the treatment arms. The AOMC control procedure comprised (1) standard optimal medical treatment and (2) 15–30 minutes psycho-oncologist-administered medical and psychosocial consultations by telephone twice per month during the active 8-week intervention phase. Assessments occurred at pre-intervention (T1) and post-intervention (T2) and 3-months post-intervention follow-up (T3). Primary outcome measurement was at T1.

Results indicated benefits for HRQoL, anxiety, and depression at T2; fatigue was not affected by either intervention. Additionally, the results suggested 3-month follow-up benefits for HRQoL and anxiety but not for depression.

These findings suggest that MBI improves various dimensions of quality of life among HSCT survivors over the short-term but does not reduce fatigue symptoms. However, this patient-preference trial should be considered a pilot study, since it is the first of its kind with HSCT, the sample size was relatively small, the design could not assess whether benefits might be sustained beyond three months, and stringent methodological controls were not possible. Nevertheless, MBI offers one of the only evidence-based approaches to enhancing quality of life for patients with serious chronic conditions, and we found no indications that it presented any adverse side-effects. Therefore, MBI should be considered for HSCT survivors who complain of poor quality of life, anxiety, or depression.

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Mueller Michael D. | **Creating and validating a patient-pertinent instrument to assess symptoms experienced related to surgical wounds in women with vulvar neoplasms – a mixed methods study (WOMAN-PRO)**
(KFS 02456-08-2009)

Post-surgery complications in women with vulvar neoplasia (vulvar intraepithelial neoplasia and vulvar cancer) are with 20–70 % still high, and no instrument assessing symptoms associated with complications existed at the beginning of this project. The research team developed and validated an instrument assessing patients' self-reported post-vulvar surgery symptom experiences.

Study aim
The mixed-method study aimed to develop and validate an instrument to assess postoperative symptom experiences in women with vulvar neoplasia (Clinical Trial: NCT01300663).

Methods and procedures
In this project we interviewed 20 patients and developed a WOMAN-PRO instrument. Content validity was tested by 6 experts and 10 patients. The psychometric properties of the instrument and the prevalence of symptoms were examined in a cross-sectional study at the university hospitals in Munich, Freiburg im Breisgau, Berlin, Düsseldorf, Zurich, Basel, and Bern, and at Cantonal Hospital St. Gallen (n = 65).

Results
Our newly developed self-report instrument WOMAN-PRO covers 31 symptoms occurring after surgery for vulvar neoplasia: 15 wound-related symptoms, 5 difficulties in daily life, and 11 aspects of psychosocial feelings, thoughts, or activities. We also examined the reliability of the instrument using a Cronbach's alpha coefficient. For wound-related symptoms alpha was 0.81, for difficulties in daily life 0.74, and 0.90 for items representing psychosocial symptoms. WOMAN-PRO allows evaluation of symptoms and symptom-related distress from women's perspective. The mean number of symptoms per woman was 20.2 (SD 5.77), with a range of 5 to 31 symptoms reported during the first week after discharge.

Conclusions and patient benefit
The data reveal a high symptom prevalence and distress, and thus call for comprehensive symptom assessment, and may allow identification of relevant topics in symptom management. A follow-up project (WOMAN-PRO II) aims to make symptom assessment a standard component of clinical practice (to promote the early detection and treatment of symptoms) and research.

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Tschudin Sibil | **Fertility preservation in young female cancer patients: assessment of needs regarding decision-making and development of a decision-aid**
(KLS 02577-02-2010)

Many young patients with cancer are confronted with impaired fertility as a consequence of their treatment. Fertility preservation has to be performed in the short time period after diagnosis and before onset of cancer treatment. Adequate counselling and support are thus of utmost importance.

Objectives
The aim of this study was to gain deeper insight into patients' motives, priorities, and conflicts during decision-making for or against any fertility-preserving procedures. Further, the study aimed to provide the basis for developing a standardized instrument that complements and supports shared decision-making on fertility preservation for young patients with cancer and their health care team.

Methods
The study addressed former and current female patients with cancer at a young age and consisted of two parts. Part 1 was an anonymous online survey, which was available via a link on cancer and fertility websites. Part 2 consisted of standardized focus groups facilitated by a psychologist.

Results
The online survey (n = 155) showed that knowledge about fertility preservation is limited. The attitudes towards fertility-preserving procedures are predominantly positive, however. The availability of helpful information was considered low. Besides their partners, the patients' physicians were the most important sources of information and support during the decision-making process.

According to the four focus groups, fertility preservation is decisive for quality of life, but it might also be connected with painful procedures as well as ethical and religious concerns. Decision-making is compromised by amount of information, pressure of time, confrontation with an already difficult and burdensome situation, and emotional involvement of family members. Intensive support by health professionals as well as decision aids such as checklists would be highly desirable.

Recommendations and patient benefit

The knowledge gained contributes to complex and ethically-demanding counselling and supports our intention to develop a decision aid for patients with cancer who might profit from fertility-preserving procedures and for the physicians responsible for their care. A subsequent research project will evaluate the clinical implementation of this tool.

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Further completed research project in 2012

Lehr Hans-Anton | KFS 02775-02-2011 | CHF 79,000.–
Institut universitaire de pathologie de Lausanne (IUP), Centre hospitalier universitaire vaudois (CHUV), Lausanne
Biomedical research on human tissues: in the twilight zone between autonomy and data protection. What do health professionals, patients and lay persons think about issues of consent and transparency in medical research, teaching, and quality control?

List of approved research projects in 2012

Total funds allocated: CHF 693,600.–

Alder Judith | KFS 02894-02-2012 | CHF 239,400.–
Abteilung für Gynäkologische Sozialmedizin und Psychosomatik, Universitätsspital Basel, Basel
Web-based counselling for families with parental cancer: a randomized controlled intervention study

Bergsträsser Eva | KFS 03008-08-2012 | CHF 189,000.–
Pädiatrische Onkologie und Pädiatrische Palliative Care, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Paediatric end-of-life care needs in Switzerland (PELICAN) study

Rosemann Thomas | KLS 02934-02-2012 | CHF 80,000.–
Institut für Hausarztmedizin, Universitätsspital Zürich, Zürich
Palliative care education in primary care

Schwappach David | KFS 02974-08-2012 | CHF 130,700.–
Stiftung für Patientensicherheit, Zürich
When silence is dangerous: "speaking up" about safety concerns in oncology

Zanetti Dällenbach Rosanna | KLS 02940-02-2012 | CHF 54,500.–
Klinik für Operative Gynäkologie und Gynäkologische Onkologie, Universitätsspital Basel, Basel
Empathy and standard diagnostic procedures in an outpatient breast clinic might not be enough

Presentation of approved research projects in 2012

Alder Judith | **Web-based counselling for families with parental cancer: a randomized controlled intervention study** (KFS 02894-02-2012)
Duration: 01. 07. 2012 – 30. 06. 2015

When a parent receives a cancer diagnosis, the whole family is affected psychologically. Several studies suggest that 30 % of patients and their partners develop clinically relevant levels of psychological symptoms. Also children of parents with cancer show a higher risk of developing emotional and behavioural problems, especially if the children are left alone to understand what is going on, if they possess insufficient coping strategies, if there is a lack of intrafamilial communication, and if parents develop adjustment problems. It has been shown that family-based counselling has a positive impact on the emotional adaptation of all family members.

Whereas in other areas of counselling the internet setting has been found to be as effective as face-to-face settings, web-based counselling has not been evaluated in the context of family-based counselling for families with parental cancer. This project aims to evaluate a web-based, interactive, and multimedia-based counselling program for this context. It includes age-specific information on cancer and cancer's impact on everyday life for children aged 3–18 years and their parents, supports the development of adequate individual and family-based coping strategies, and thereby considers the known risk factors for maladaptation.

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Bergsträsser Eva | **Paediatric end-of-life care needs in Switzerland (PELICAN) study** (KFS 03008-08-2012)
Duration: 01. 06. 2012 – 31. 05. 2015

Despite of enormous advances in paediatric oncology, death remains a reality for at least 20 % of children with cancer. The overarching aim of the nationwide PELICAN study is to provide comprehensive information and understanding about the current practice of end-of-life (EOL) care in children dying of cancer. How and where are these children dying (at home or in hospital), and what are the problems, needs, and perspectives of parents and health care professionals?

These questions need to be addressed to improve EOL care of children in Switzerland. This study uses quantitative and qualitative inquiry methods: (1) patient charts of children (aged 0–18 years) who died in 2011 and 2012 will be analysed, (2) all parents of these children will be asked to participate in a questionnaire survey, and (3) to also include consideration of the experiences and needs of those who provide EOL care of children, health care professionals will be invited to participate in group interviews. With this study, urgently needed information will become available for development and implementation of a needs-driven concept of paediatric EOL care in Switzerland.

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Rosemann Thomas | **Palliative care education in primary care** (KLS 02934-02-2012)
Duration: 01. 01. 2013 – 31. 12. 2014

Despite many efforts to improve palliative care in Switzerland, many patients suffer from pain and reduced quality of life when they are in a palliative situation. It is assumed that this is due to a lack of coordination between the caring institutions (general practitioner (GP), oncologist, Spitex, further nurses) and to a lack of knowledge on the part of some GPs regarding pain treatment. Do patients treated by a GP specially educated in coordinating and providing palliative care suffer less pain and have a higher quality of life (QoL) at the end of their life?

First, a qualitative study will be conducted to assess barriers and facilitators for a better coordination of care and improved pain treatment. All providers actually involved in palliative care will be interviewed. Based on these results, a tailored intervention addressing the identified barriers and facilitators will be created. Later, in a randomized controlled trial, QoL and pain of 70 patients treated by a specially educated GP will be compared with 70 patients treated by a regular GP. Overall, 40 GPs, 20 in each group, will participate. We assume that patients in the intervention group will suffer less and have higher QoL. If our hypotheses are confirmed, the education developed should be provided to as many GPs as possible to improve QoL of patients in a palliative situation.

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Schwappach David | **When silence is dangerous: "speaking up" about safety concerns in oncology** (KFS 02974-08-2012)
Duration: 01.02.2013 – 31.03.2014

Adverse events in oncology care pose a serious threat to cancer patients. To prevent errors, communication among health care professionals is essential. This study addresses communication within oncology teams – namely, whether and how team members communicate safety concerns and speak up. Incident reporting systems confirm that staff often notes team members' errors and bypassed safety rules. These situations usually have no severe consequences for patients. Oncology staff will be surveyed using qualitative interviews and a self-administered questionnaire. We will investigate how, and how frequently, physicians and nurses speak up about errors and risky behaviours, and examine which factors explain this behaviour. Understanding why professionals in oncology speak up or choose to remain silent will provide opportunities for learning in oncology care and contribute to a safety culture. Only if errors and risky behaviours are openly discussed within oncology teams can measures be taken to improve the quality of care provided.

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Zanetti Dällenbach Rosanna | **Empathy and standard diagnostic procedures in an outpatient breast clinic might not be enough** (KLS 02940-02-2012)
Duration: 01.07.2012 – 30.06.2015

Having to have a breast biopsy taken due to suspected breast cancer is an emotionally exceptional situation because of the biopsy itself and because of the threat of a cancer diagnosis. Study findings suggest that the level of anxiety associated with breast biopsies is higher compared to the level of anxiety preceding other interventions or operations. Doctors and nurses at the outpatient breast clinic at Basel University Hospital are empathetic and try to address anxiety and give emotional support before, during, and after a necessary breast biopsy. Nevertheless, we are convinced that we could reduce the women's level of anxiety by giving them structured and standardized information.

The project focuses on improving the patients' knowledge about the procedure of breast biopsy by giving patients' a take-home brochure and by meeting their emotional need to reduce anxiety related to the biopsy by giving them structured and standardized information. The structured and standardized information about the biopsy is provided by the physician who performs the biopsy and who has had psychological training for this purpose. If we can demonstrate that the interventions can reduce anxiety related to breast biopsy, we will implement them in daily clinical practice.

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Researching the long-term effects of childhood cancer

Fortunately, cancer is rare in children and adolescents. Only one per cent of all cases occur before age 21; in Switzerland there are approximately 300 new cases per year. Nevertheless, cancer is the second leading cause of death in children (the first is accidents). When children develop cancer, many potential years of life are affected. Therefore, the aim of paediatric oncology should not only be to cure children and adolescents with cancer; the survivors also want to have a life without adverse late effects, a life with normal development and schooling, and a normal working and family life.

Common types of childhood cancers

Children have different cancers than adults. Common cancers in adulthood are carcinomas such as breast, lung, prostate, cervical, colon, and skin cancer. Childhood cancers are mostly leukaemias, lymphoma, brain tumours, bone and soft tissue sarcomas, and a number of cancers of the immature embryonic tissues, such as retinoblastoma, neuroblastoma, nephroblastoma (kidney), hepatoblastoma (liver), and germ cell tumours (Figure 1). Treatment of children differs as well. Children tolerate higher doses of some chemotherapy drugs than adults, but their immature organs that are still in development have to be specially protected (for example, the brain and the reproductive organs).

Prof. Claudia E. Kuehni, MD
Director of the Swiss Childhood Cancer Registry and research group head at the Institute of Social and Preventive Medicine, University of Bern

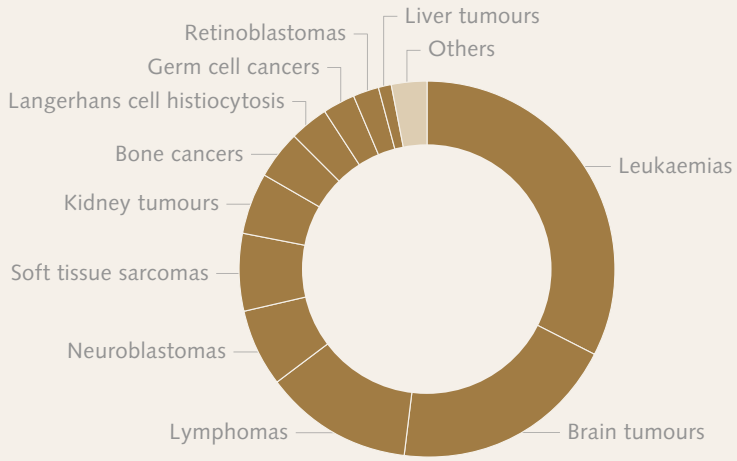
Corina S. Rueegg, PhD
Project manager of the Swiss Childhood Cancer Survivor Study at the Institute of Social and Preventive Medicine, University of Bern

With the great number of different tumours and the rare occurrence of childhood cancers, treating health care professionals must possess great expertise to assure correct diagnosis, treatment, and documentation. For this reason, all treating physicians are closely networked in the framework of the Swiss Paediatric Oncology Group (SPOG), and for almost 40 years, data on children with cancer has been registered at the national level in the Swiss Childhood Cancer Registry.[1]

Late effects after successful treatment

Thanks to advances in treatment and diagnosis, especially the standardized treatment of practically all patients in international treatment optimization studies, over 80 per cent of children with cancer can be cured today. In the 1970s this figure was less than 60 per cent (Figure 2). However, longitudinal studies in the United States and Great Britain have shown that about two-thirds of successfully treated children develop adverse late effects, such as secondary tumours, endocrine disorders, hardness of hearing, blindness, fertility problems, and cardiovascular and pulmonary or also mental health problems. These late effects can occur years or decades after the successful treatment for childhood cancer. For this reason, it is important that clinical observation and related research is not discontinued five or 10 years

Figure 1
Relative frequency of different types of childhood cancers



after the end of treatment. Possible late effects should be detected early, treated, and if possible avoided for future patients. With the Swiss Childhood Cancer Registry, therefore, long-term follow-up and intensive research on long-term outcomes are conducted.

The Swiss Childhood Cancer Survivor Study

The Swiss Childhood Cancer Survivor Study (SCCSS) is a study conducted by the Swiss Childhood Cancer Registry and the SPOG; it is based at the Institute of Social and Preventive Medicine at the University of Bern. The study aims to investigate late effects after treatment for childhood cancer and their risk factors. The research findings contribute toward continuous improvement of treatment and follow-up of children with cancer.

Included in the study are all children in Switzerland who since 1976 had cancer between the ages of 0 and 15 and survived for more than five years.[2] They all receive an information letter from the clinic at which they were treated as well as a detailed questionnaire in German, French, or Italian. The questionnaire contains items on quality of life, physical health and health behaviours, medications and doctor visits, mental health, experience of cancer, education, occupation, and fertility and starting a family. Some sections of the questionnaire are adapted to the age of the respondents (children, adolescents, adults). For purposes of comparison, the questionnaire is also sent to a sample of siblings.

Current status of the study

The first round of the SCCSS has been successfully completed, and the data obtained are being analysed and published on an ongoing basis. In total, 3,377 former child patients with cancer met the inclusion criteria. A questionnaire could be sent to 2,962 of these persons; 2,192 respondents returned the questionnaire (74 per cent). Of these, 1,274 were adults, 458 were adolescents, and 460 were children. In addition, 827 siblings (54 per cent of those contacted) returned a questionnaire. Up to now, data on mainly adolescent and adult survivors has been analysed, as the youngest participants were contacted last. All publications are listed on the website of the Swiss Childhood Cancer Registry (www.kinderkrebsregister.ch).

Most of the survivors in good health

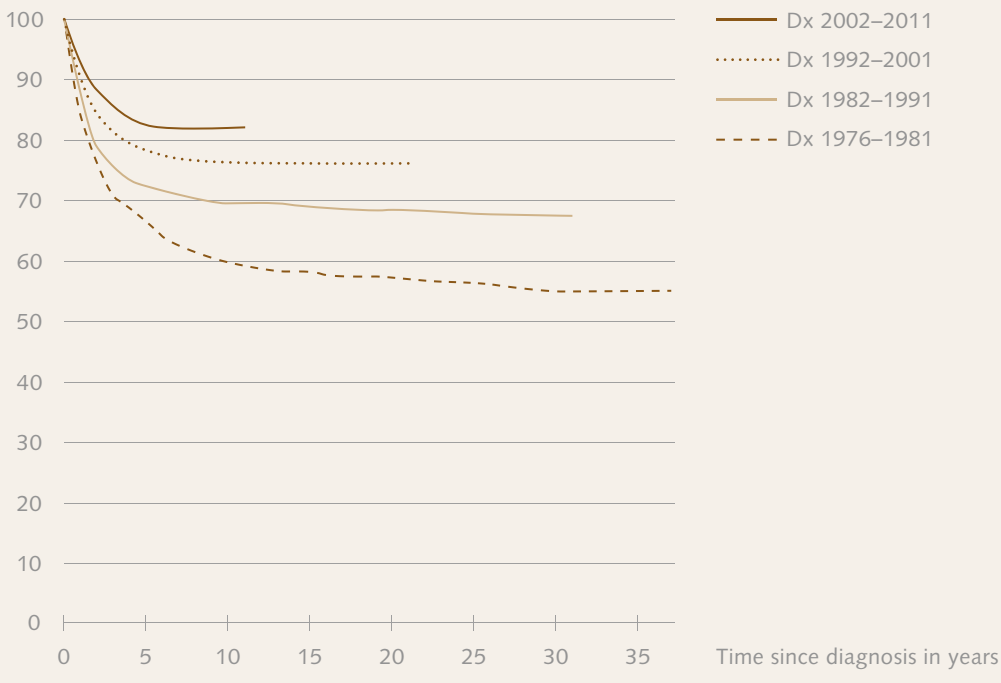
Fortunately, most of the survivors of childhood cancer are doing well. For example, the subjective quality of life of the survivors (assessed using the SF-36 Health Survey) is comparable to that of the norm population,[3] even that of children who had a recurrence of leukaemia and had to undergo long and intensive treatment.[4] Survivors had lower scores only in the areas of physical functioning in everyday life (walking, climbing stairs, getting dressed, getting washed, etc.).[3-5] Due to the long and intensive treatment, they often had some delay completing school and training, but the level of education that they attained in the end was comparable to healthy controls.[6] On average, childhood cancer survivors do not have mental health problems more frequently than healthy persons of the same age or their siblings.[7,8]

Groups with higher risk of late effects

Despite these welcome results, some groups were found to have a higher risk of late effects and chronic diseases, such as impaired vision, musculoskeletal and neurological problems, obesity, or memory impairment. This was especially true for survivors of brain, bone, and eye tumours (retinoblastomas). These functional disorders were connected with reduced quality of life, limitations in everyday life, and more mental health problems.[3-8]

As a healthy lifestyle and early treatment alleviate many late effects and can also prevent some of them in part, a healthy lifestyle is particularly important for all survivors. The physical activity of the study respondents was comparable to the norm population, but like healthy persons of the same age, only 50 per cent of the survivors had as much physical activity as is recommended by the Federal Office of Sport.[9] Happily, survivors of childhood cancer smoke less than the average for Switzerland, but as adolescents and young adults they drink excessively more often (binge drinking).[10,11]

Figure 2
Change in survival rates in children with cancer in Switzerland from 1976 to 2011 (Dx = year of diagnosis)



Applying the results to the benefit of persons with childhood cancer

The SCCSS has shown that much has been done in the last four decades in Switzerland to optimize chances of curing cancer and to minimize late effects after cancer in childhood. The risk factors found for late effects will aid continued improvement of the treatment and care of persons with childhood cancer in future. For the especially vulnerable patient groups identified, closer follow-up is appropriate. Through close cooperation between the Swiss Childhood Cancer Registry, the SPOG, and patient organizations in this late-effects study, the research findings can be implemented in clinical practice and thus benefit patients immediately.

Risk-adapted after care, which is recommended in international guidelines, can contribute towards reducing late effects after treatment of childhood cancer. In Switzerland today, it was found that only 23 per cent of adult and 56 per cent of adolescent survivors attend regular follow-ups.[12,13] The reason was that the benefit of follow-up examinations was often not clear to the survivors.[14] These findings and further research projects on after care of persons with childhood cancer and their care in adulthood make concrete contributions towards development of a national after-care model for Switzerland.

Prof. Claudia E. Kuehni, MD

Claudia Kuehni studied medicine at the University of Bern and then completed training as a medical specialist in paediatrics and paediatric pneumology in St. Gallen, Delémont, Leicester (UK), and Bern. In parallel, Kuehni began research activities in paediatric epidemiology. She completed a Master's degree in epidemiology in London (UK) in 1998. Since 2002 she has headed a research group, taught, and directed the Swiss Childhood Cancer Registry at the Institute of Social and Preventive Medicine at the University of Bern. In 2011 she was appointed associate professor at the University of Bern. She is currently heading a large research programme on the causes and treatment of childhood diseases, with a focus on respiratory diseases and cancer.

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Corina S. Rueegg, PhD

Corina Rueegg studied sport sciences in the areas of prevention and rehabilitation at the University of Basel. In 2012 Rüegg completed a doctorate in epidemiology and biostatistics at the Institute of Social and Preventive Medicine at the University of Bern, with a dissertation on physical activity and functioning of survivors of childhood cancer. Since 2009 she has been the project manager of the Swiss Childhood Cancer Survivor Study (SCCSS), a longitudinal study investigating several issues, including physical activity, weight, and quality of life.

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List of completed research projects in 2012

Bouchardy-Magnin Christine | OCS 02070-04-2007 | CHF 342,900.–
Registre genevois des tumeurs, Institut de médecine sociale et préventive, Université de Genève, Genève
Epidemiological research on the impact of genetic factors in breast cancer occurrence, treatment and outcomes in Geneva using population-based data from the first Familial Breast Cancer Registry in Switzerland

Levi Fabio | KFS 02437-08-2009 | CHF 270,000.–
Unité d'épidémiologie du cancer, Institut universitaire de médecine sociale et préventive Lausanne, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Modelling, interpretation and forecasting of cancer mortality in Europe

Meier Christoph | KLS 02737-02-2011 | CHF 88,000.–
Spital-Pharmazie, Universitätsspital Basel, Basel
Use of metformin and the risk of colorectal, pancreatic, ovarian, and lung cancer

Mullis Primus | KLS 02586-02-2010 | CHF 184,300.–
Abteilung für Pädiatrische Endokrinologie, Diabetologie und Stoffwechsel, Universitätsklinik für Kinderheilkunde, Inselspital, Universitätsspital Bern, Bern
Risk of cancer and long-term mortality in children treated with growth hormone: Swiss participation in the EU FP7 project "Safety and Appropriateness of Growth Hormone Treatment in Europe" (SAGhE)

Pestalozzi Bernhard | KLS 02738-02-2011 | CHF 127,100.–
Klinik für Onkologie, Universitätsspital Zürich, Zürich
End-of-life delivery of care patterns in cancer patients in Switzerland

Vounatsou Penelope | KLS 02393-02-2009 | CHF 215,850.–
Biostatistics Unit, Departement für Epidemiologie und Public Health, Schweizerisches Tropen- und Public Health-Institut, Basel
Spatio-temporal patterns and forecasting of gender-specific lung and other tobacco-related cancer mortality and morbidity rates in Switzerland

Presentation of completed research projects in 2012

Bouchardy-Magnin Christine | **Epidemiological research on the impact of genetic factors in breast cancer occurrence, treatment and outcomes in Geneva using population-based data from the first Familial Breast Cancer Registry in Switzerland** (OCS 02070-04-2007)

Breast cancer is a public health priority. The French-speaking cantons of Switzerland have among the highest incidence risks of developing breast cancer worldwide. The familial history of breast cancer is one of the best-known risk factors of the disease. Approximately 10 % of breast cancers are of hereditary origin. Thanks to financial grants from the Swiss and Geneva Cancer Leagues, the Geneva Cancer Registry started the first Familial Breast Cancer Registry in Switzerland in 2001. The unique data from the Familial Breast Cancer Registry enable multiple studies on hereditary breast cancer.

Study objectives
Our main objectives were to determine the impact of heritability on method of diagnosis, treatment, prognosis, and the risk of second cancer occurrence after breast cancer.

Method and proceeding
Since 1990, for breast cancer patients resident in the canton of Geneva we have collected data on familial cancer occurrence in addition to method of detection, tumour characteristics, treatment, and survival. The Familial Breast Cancer Registry consists of more than 7,000 patients. Using this dataset, we have been able to compare breast cancer patients without a family history of breast cancer with patients with a high familial risk.

Study results
The Familial Breast Cancer Registry enabled us to conduct numerous studies between 2008 and 2012. We found that women with high familial risk of breast cancer were more often diagnosed with early stage tumours and received more aggressive treatments. We also showed that these patients have a higher risk of developing a second cancer and identified the factors that influence this excess risk. Moreover, and for the first time, we observed that breast cancer prognosis might have a hereditary component that is not linked to tumour characteristics or treatments received.

Patient benefit
Thanks to these innovating research projects, we have been able not only to determine the impact of heritability on the disease but also to better understand the genetic mechanisms influencing prognosis and the risk of second cancer occurrence. These research projects – and many others to come – will ultimately improve the quality of surveillance and care of women with a high familial risk of breast cancer.

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Levi Fabio | **Modelling, interpretation, and forecasting of cancer mortality in Europe** (KFS 02437-08-2009)

The main objective of this project, which started in 1992, is to maintain and improve the integrated system for analysing, modelling, and interpreting mortality statistics in Europe created by our international collaborative group.

Overall, cancer mortality in Europe (and in Switzerland) has been declining, although to various degrees, since the early 1990s, and it is likely to further decrease in the near future. Major determinants of these favourable trends are the decreases in lung and other tobacco-related cancers in men, steady decreases in gastric cancer, and more recent ones in colorectal cancers. Among women, substantial favourable contributions are from decreases in cervical cancer and more recent ones of mortality from breast cancer, particularly in Northern and Western Europe. According to new projections, lung cancer mortality is likely to overtake breast cancer as the main cause of cancer death among European women by the middle of this decade.

Monitoring past and predicting (short-term) future trends in cancer mortality provides important public health information, helps measure the success of implemented preventive strategies, and identifies priorities for cancer prevention and management. It can also generate hypotheses to be tested in analytical studies and provide support, or lack thereof, of hypotheses generated elsewhere.

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Meier Christoph | **Use of metformin and the risk of colorectal, pancreatic, ovarian, and lung cancer**
(KLS 02737-02-2011)

In a series of case-control analyses using the General Practice Research Database (GPRD), we explored the risk of developing incident colorectal, pancreatic, ovarian, and lung cancer in association with the use of metformin or other anti-diabetic drugs.

Results

Metformin and colorectal cancer

We studied 920 diabetic patients with colorectal cancer. Mean age (± SD) was 70.2 ± 8.6 years, and 63.3 % were male. Extensive use (≥ 50 prescriptions) of metformin was associated with a slightly increased risk of colorectal cancer (adj. OR 1.43, 95 % CI 1.08–1.90) as compared to non-use. Neither extensive use of sulfonylureas (adj. OR 0.79, 95 % CI 0.60–1.03) nor insulin (adj. OR 0.90, 95 % CI 0.63–1.28) was associated with an increased risk of colorectal cancer.

Metformin and pancreatic cancer

We identified 2,763 case patients with a recorded diagnosis of pancreatic cancer. Mean age (± SD) was 69.5 ± 11.0 years, and 46.2 % were male. Long-term use (≥ 30 prescriptions) of metformin was not associated with a materially altered risk of pancreatic cancer (adj. OR 0.87, 95 % CI 0.59–1.29). Use of sulfonylureas (≥ 30 prescriptions, adj. OR 1.90, 95 % CI 1.32–2.74) and use of insulin (≥ 40 prescriptions, adj. OR 2.29, 95 % CI 1.34–3.92) was associated with an increased risk of pancreatic cancer.

Metformin and ovarian cancer

We identified 1,611 case patients with a recorded diagnosis of ovarian cancer. Mean age (± SD) was 61.2 ± 13.1 years. Use of ≥ 10 prescriptions of metformin was associated with a statistically significantly decreased risk of ovarian cancer (adj. OR 0.38, 95 % CI 0.18–0.81). Use of sulfonylureas was not associated with an altered risk of ovarian cancer (adj. OR 1.26, 95 % CI 0.65–2.44). Long-term use of insulin (≥ 40 prescriptions) was associated with a slightly increased risk for ovarian cancer (adj. OR 2.29, 95 % CI 1.13–4.65).

Metformin and lung cancer

We identified a total of 13,043 cases with incident lung cancer. Mean age (± SD) was 69.0 ± 10.3 years, and 58.2 % were male. Long-term use (≥ 40 prescriptions) of metformin was not associated with an altered risk of lung cancer (adj. OR 1.21, 95 % CI 0.97–1.50). Use of sulfonylureas or insulin was not associated with a decreased risk of lung cancer.

Conclusions
Metformin may be of interest for chemoprevention of ovarian but not colorectal, pancreatic, or lung cancer.

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Mullis Primus | **Risk of cancer and long-term mortality in children treated with growth hormone: Swiss participation in the EU FP7 project "Safety and Appropriateness of Growth Hormone Treatment in Europe" (SAGhE)** (KLS 02586-02-2011)

Recombinant human growth hormone (rhGH) was initially used to treat cases of primary severe growth hormone deficiency (GHD), but its uses have multiplied. GHD is the most common endocrine late effect after childhood cancer and/or cancer treatment. However, there are concerns about cancer risk and long-term mortality. Good long-term studies on the safety of rhGH replacement therapy are lacking.

Aim
Switzerland is participating in a large European study that investigates the long-term impact of rhGH therapy on adult height, quality of life, cancer incidence, and mortality.

Method and procedure
We collected medical data from patient files in the hospitals. Information about quality of life and current health status was assessed with questionnaires. We compared our population to cancer registries and mortality statistics of the Swiss Federal Statistical Office (FSO) to obtain information about cancer incidence and mortality.

Results
We identified 1,684 patients treated with rhGH in Switzerland during childhood. 754 patients were older than 18 years by 1 March 2011 and thus eligible for the SAGhE study. We finished medical data collection for most of those patients. Of 639 contacted persons, 383 (60 %) returned a questionnaire. Fourteen patients have died. For those, we obtained death certificates from the FSO. We linked our dataset with the Swiss Childhood Cancer Registry (SCCR) and two cantonal cancer registries and found four patients who had been diagnosed with a malignant cancer after rhGH treatment had begun. The anonymized data has been delivered to the European SAGhE consortium. A continuation of the project until December 2013 has been approved (KLS 02948-02-2012), and publications are expected in 2013 and 2014.

Patient benefit
Results will aid the adaptation of recommendations for treatment with rhGH in children to guarantee long-term safety for current and future patients. For former patients, preventive medical check-ups can be planned.

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Pestalozzi Bernhard | **End-of-life delivery of care patterns in cancer patients in Switzerland**
(KLS 02738-02-2011)

Treatment patterns and treatment intensity towards the end of life of cancer patients are to a large extent unexplored in Switzerland. Health insurance data, which contain a rather complete summary over all insured medical services provided to a patient, are well suited for examination of treatment paths and patterns. This study was a retrospective cohort study. First, with the help of the cancer registries BL/BS, TI, VS, and ZH, patients insured by the health insurer Helsana who died between 2006 and 2008 were identified as cancer patients. For these identified cancer patients, we examined where, how, and how long they were treated in the last 1 to 6 months before death. The goal was to analyse whether cancer type, age, gender, or regional differences can be observed. In addition, this study described an "as-is" state that can, after the introduction of the Swiss DRGs, serve as a reference for future comparison.

Results and patient benefit
Starting with insured patients having died in 2006–2008 (n = 47,769), we identified in cancer registries a total of 3,873 cancer patients with the following distribution: in cantons BL/BS 378 (9.8 %), TI 926 (23.8 %), VS 363 (9.4 %), ZH 2,142 (55.3 %), other 64 (1.7 %). At the time of death 2,640 (68.2 %) were hospitalized, of which 2,567 were patients in our cantons. Of these deaths, 2,086 (81 %) were cancer related, whereas 408 (16 %) were non cancer related; in 73 (2.8 %) there was no information.

Demographic data included age, gender, in-patient versus out-patient status, type of institution, cancer diagnosis (lung, colon, breast, prostate, other). Most important are the data on chemotherapy, radiotherapy, and surgery during the last three months of life. Using this large dataset, it was possible to describe where and how patients were treated. For example, three months before death only 10 % of patients were hospitalized in an acute care facility, a proportion which continuously increased to 54 % at the time of death. About 10 % of cancer patients were treated with chemotherapy in the last month of their life, with considerable geographic variation among the cantons.

These and similar findings have not been previously gauged empirically in Switzerland. In addition, our study represents a point of reference for comparison with other countries or future investigations. We want to state very clearly that it is not possible to make any value judgements on the appropriateness of treatments and of care delivered based on these data.

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Vounatsou Penelope | **Spatio-temporal patterns and forecasting of gender-specific lung and other tobacco-related cancer mortality and morbidity rates in Switzerland** (KLS 02393-02-2009)

Around 85–90 % of all lung cancer deaths are estimated to be attributed to active or passive smoking. In Switzerland, lung cancer is the first cause of cancer mortality in men and second in women (after breast cancer). In this project, Bayesian spatio-temporal models were applied to analyse Swiss tobacco-related cancer data, considering past as well as future trends. We also estimated incidence for cantons without cancer registries and developed (indirect) proxies for the spatial distribution of the smoking prevalence.

Study aim
This project aimed to (1) produce countrywide smoothed maps of tobacco-related cancer mortality since 1969, (2) assess gender-specific differences of cancer mortality rates among language and urbanization regions, (3) determine geographical patterns of tobacco-related cancer mortality up to 2018, (4) estimate comprehensive cantonal incidence, and (5) develop indirect approximation of countrywide smoking prevalence.

Methods and approaches
Bayesian spatio-temporal models were applied to estimate age and gender-specific tobacco-related cancer mortality in Switzerland from 1969 to 2002. Furthermore, Bayesian age-period-cohort (APC) models were applied to project Swiss gender-specific tobacco-related cancer mortality at the national level and for each language region in Switzerland (German, French, and Italian). Back-calculation models were developed to estimate incidence from observed mortality and estimated survival distribution. In addition, Bayesian spatial negative binomial regression models were applied on lung cancer mortality to approximate spatial smoking behaviour.

Results
Countrywide smooth maps highlighted gender-specific temporal and spatial trends (high female mortality in urban areas; mortality for males rather homogeneous). The estimation of countrywide incidence was based on developed and validated models. Projections up to 2018 showed an increasing trend of tobacco-related cancer mortality for women.

Recommendations and patient benefit
The produced maps of countrywide cancer mortality offer an intuitive insight into the spatial distribution of the disease and are helpful for interventions such as the National Tobacco Programme. The estimated lung cancer incidence provides information for cantons without cancer registries and for past decades. Projections, which predict increasing mortality rates (such as for Swiss women), might have a sensitizing effect.

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List of approved research projects in 2012

Total funds allocated: CHF 2,133,700.–

Bodmer Michael | KFS 02990-08-2012 | CHF 84,100.–
Abteilung für Pharmakoepidemiologie, Spital-Pharmazie, Universitätsspital Basel, Basel
Use of metformin and other anti-diabetic drugs and the risk of endometrial, thyroid, and head and neck cancer

Bouchardy-Magnin Christine | KFS 02946-02-2012 | CHF 302,500.–
Registre genevois des tumeurs, Institut de médecine sociale et préventive, Université de Genève, Genève
Impact of genetic and familial factors on breast and other cancers occurrence, treatment, and outcomes. Studies from the first population-based Familial Breast Cancer Registry in Switzerland

Bucher Heiner C. | KFS 03039-08-2012 | CHF 151,900.–
Institut für Klinische Epidemiologie und Biostatistik, Universität Basel, Basel
Chronic hepatitis B and C co-infection and risk for the development of non-Hodgkin's lymphoma in HIV-infected patients: a multinational cohort study

Clough-Gorr Kerri | KLS 02936-02-2012 | CHF 250,400.–
Nationales Institut für Krebsepidemiologie und -registrierung (NICER), Institut für Sozial- und Präventivmedizin, Universität Zürich, Zürich
Patterns of care study (POC): a comprehensive national examination of prostate cancer in Switzerland 2006–2010

Egger Matthias | KFS 02997-08-2012 | CHF 249,900.–
Institut für Sozial- und Präventivmedizin (ISPM), Universität Bern, Bern
Screening for anal cancer in HIV-infected homosexual men in Switzerland? Mathematical modelling study

Keiser Olivia | KFS 02938-02-2012 | CHF 249,900.–
Institut für Sozial- und Präventivmedizin (ISPM), Universität Bern, Bern
Screening and treatment for hepatitis C and hepatocellular carcinoma: individual-based simulation model

Misselwitz Benjamin | KFS 02977-08-2012 | CHF 250,500.–
Klinik für Gastroenterologie und Hepatologie, Universitätsspital Zürich, Zürich
Microsimulation and mathematical modelling of the natural history of colorectal cancer for optimal screening strategies

Mullis Primus | KLS 02948-02-2012 | CHF 165,000.–
Abteilung für Pädiatrische Endokrinologie, Diabetologie und Stoffwechsel, Universitätsklinik für Kinderheilkunde, Inselspital, Universitätsspital Bern, Bern
Risk of cancer and long-term mortality in children treated with growth hormone: Swiss participation in the EU FP7 project "Safety and Appropriateness of Growth Hormone Treatment in Europe" (SAGhE)

Rohrmann Sabine | KFS 03048-08-2012 | CHF 262,000.–
Institut für Sozial- und Präventivmedizin (ISPM), Universität Zürich, Zürich
Modifiable risk and protective factors of cancer – a population based approach in Switzerland

Spycher Ben D. | KFS 03049-08-2012 | CHF 167,500.–
Institut für Sozial- und Präventivmedizin (ISPM), Universität Bern, Bern
The role of population mixing and exposure to infections in the aetiology of childhood leukaemia: a national cohort study

Presentation of approved research projects in 2012

Bodmer Michael | **Use of metformin and other anti-diabetic drugs and the risk of endometrial, thyroid, and head and neck cancer** (KFS 02990-08-2012)
Duration: 01.10.2012 – 31.03.2014

In recent years, a mounting body of evidence has suggested that use of metformin exerts protective effects against development and growth of different malignant neoplasms. Despite the availability of limited evidence from basic science studies, no observational data are currently available linking the use of metformin to an altered risk of endometrial cancer, thyroid cancer, and head and neck cancer.

Using the well-known General Practice Research Database (GPRD), we will conduct a series of case-control analyses to explore the risk of endometrial cancer, thyroid cancer, and head and neck cancer in association with the use of metformin, other oral anti-diabetic drugs, and insulin. If our study provides evidence of a protective effect of metformin, this drug may be further tested in clinical trials for chemoprevention and/or treatment for the respective malignancy.

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Bouchardy-Magnin Christine | **Impact of genetic and familial factors on breast and other cancers occurrence, treatment and outcomes. Studies from the first population-based Familial Breast Cancer Registry in Switzerland** (KFS 02946-02-2012)
Duration: 01.08.2012 – 31.07.2014

For the years 2012–2014, our research projects aim to determine how many women at risk profit from genetic counselling and the impact of such counselling on care, treatment, and prognosis. We also aim to assess whether family history modifies the effect of treatment and prognosis factors, and if the efficacy of treatment is the same for women with and without high familial risk. We will also examine the risk of breast cancer and/or other cancers among first-degree relatives. Finally, we will evaluate if familial risk factors influence male breast cancer, a very rare disease.

We are going to analyse additional data on other types of cancer in the family history. We are also going to link our database with other datasets from the Geneva University Hospitals and the Cantonal Population Office to obtain information on oncogenetic consultation and kinship. We will examine data on men with breast cancer to determine the impact of their family history. Finally, we will compare and evaluate the risk of cancer among the first-degree relatives of affected women with the risk observed in the general population.

These fascinating research projects will help us to enhance our knowledge on the impact of heredity on breast cancer, and to better understand the genetic factors that could modify the prognosis of the disease, with the main objective of improving surveillance and care for women and men at high risk of breast cancer. This accepted project is the continuation of the completed projects OCS 02070-04-2007 and KFS 02544-02-2010.

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Bucher Heiner C. | **Chronic hepatitis B and C co-infection and risk for the developement of non-Hodgkin's lymphoma in HIV-infected patients: a multinational cohort study** (KFS 03039-08-2012)
Duration: 01.03.2013 – 28.02.2015

Non-Hodgkin's lymphoma (NHL) remains the most important AIDS-related condition since the successful introduction of anti-retroviral therapy. The risk of NHL in successfully treated HIV-infected individuals is still higher than for HIV-uninfected individuals of the same age. The prognosis of NHL in HIV-infected patients remains serious and is poorer than in HIV-uninfected individuals, although much progress has been made in the treatment of NHL in HIV-infected individuals. Chronic infections with hepatitis B (HBV) and C (HCV) are now increasingly recognized as important co-factors in the development of NHL in HIV-negative individuals. Many individuals with HIV infection are also chronically infected with HBV and HCV, because these viruses share the same routes of transmission. To what extent co-infection with HBV and HCV contributes to the higher risk of NHL in HIV infection is unclear.

This international multi-cohort project intends to investigate the risk of NHL HIV-infected patients with chronic hepatitis B and C infection. Knowledge about the association of HBV and HCV co-infection in HIV infection is important for the further development of optimized treatment strategies for these co-infections and for development of strategies to reduce the most common AIDS condition in the era of anti-retroviral therapy.

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Clough-Gorr Kerri | **Patterns of care study (POC): a comprehensive national examination of prostate cancer in Switzerland 2006–2010** (KLS 02936-02-2012)
Duration: 01. 07. 2012 – 30. 06. 2014

From 1980 through 2008 prostate cancer mortality was second after lung cancer in men in Switzerland. With an age-standardized estimated rate of 83.8 per 100,000 residents, Switzerland had one of the highest prostate cancer incidence rates in the world. The aim of the study is to generate the first national population-based prostate cancer-specific treatment evidence in Switzerland. This retrospective population-based prostate cancer patterns of care study with up to 5 years of follow-up focuses on dissemination of treatment modalities, variations in care, impact of treatment, and short-term survival.

Analyses will: (1) evaluate 1- to 5-year all-cause and prostate cancer-specific mortality utilizing a broad vector of factors known to influence survival; (2) identify patient, tumour, and systemic characteristics associated with receipt of treatments; and (3) compare the effectiveness of active treatment versus active surveillance in preventing early poor treatment response, adjusting for co-morbidity, tumour characteristics, geo-linguistic region, and demographic characteristics. This study will provide much needed data to answer questions about treatment disparities and guide clinicians' and policymakers' understanding of the current state of prostate cancer care and how to improve the quality of future care in Switzerland.

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Egger Matthias | **Screening for anal cancer in HIV-infected homosexual men in Switzerland? Mathematical modelling study** (KFS 02997-08-2012)
Duration: 01. 01. 2013 – 31. 12. 2014

HIV-infected men who have sex with men (MSM) have an increased risk of anal cancer. The most important risk factor is immunosuppression and in particular a low nadir CD4 positive T-cell count (i. e. lowest ever CD4 count). Precursors of anal cancer can be detected by different screening interventions, and progression from precancerous lesions to anal cancer can be slowed down or prevented by ablative and/or topical treatment. However, the feasibility, cost-effectiveness, and potential harms of systematic screening are unclear at present.

We aim to develop an individual-based mathematical simulation model to model anal cancer incidence in HIV-infected MSM in Switzerland. The model will be used to compare the benefits, harms, and costs of different screening and treatment strategies, taking into account the nadir CD4 and the time since reaching the nadir. The findings will provide guidance on whether and how screening should be implemented in Switzerland and other countries to maximize the individual-level and population-level benefit. An "individual-based stochastic simulation model" will be developed using data from a large longitudinal study of patients infected with HIV: the Swiss HIV Cohort Study (SHCS). The SHCS is one of the oldest HIV cohort studies worldwide; currently 70 anal cancers are documented in the SHCS.

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Keiser Olivia | **Screening and treatment for hepatitis C and hepatocellular carcinoma: individual-based simulation model** (KFS 02938-02-2012)
Duration: 01. 02. 2013 – 31. 01. 2015

Hepatitis C virus (HCV) is a major cause of liver disease worldwide and a source of high morbidity and mortality. In particular, HCV is one of the main causes of hepatocellular carcinoma (HCC), which is among the most frequent causes of cancer death and one of the least curable malignancies worldwide. Potential interventions to reduce HCC include intensified HCV screening strategies and early therapeutic interventions. New treatment options improve treatment success and could reduce HCC incidence. However, the efficacy of these interventions to reduce the burden of HCC remains unknown.

We aim to develop an individual-based, mathematical model of the impact of anti-viral drugs and screening interventions on HCC development in Switzerland. The model will be parameterized with data from the Swiss Hepatitis C Cohort study (SCCS). The cohort provides detailed information on risk factors for HCV and progression to HCC and outcomes among HCV infected patients. We previously constructed a mathematical model to simulate the progression of HIV infection during antiretroviral therapy. We will adapt this model for HCV infection.

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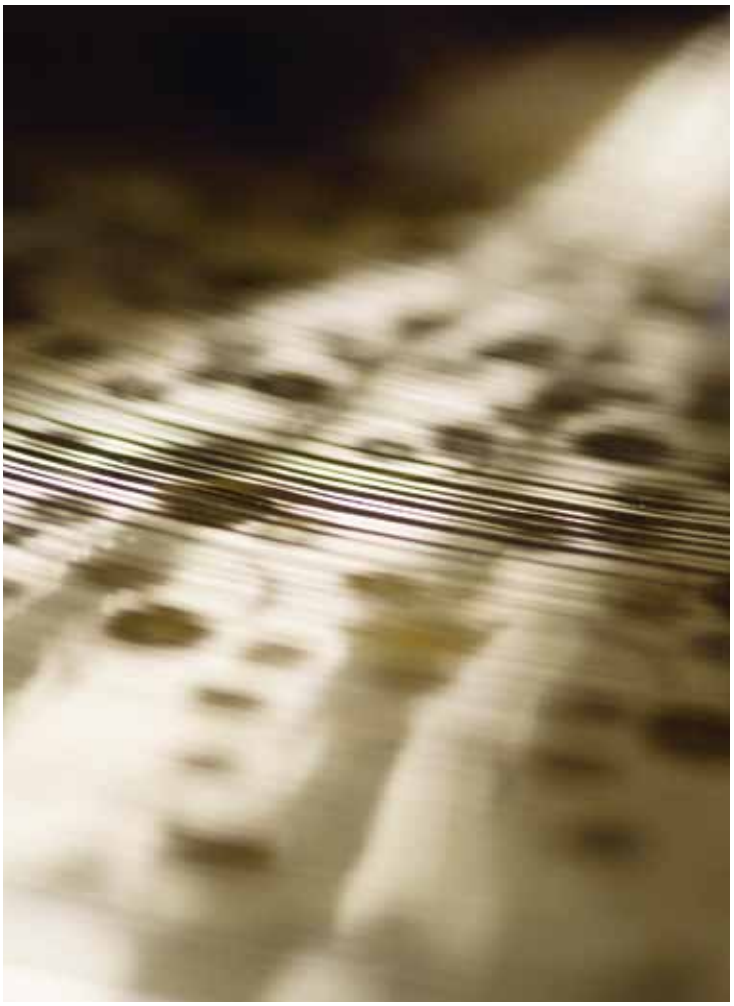

Misselwitz Benjamin | **Microsimulation and mathematical modelling of the natural history of colorectal cancer for optimal screening strategies**

(KFS 02977-08-2012)

Duration: 01.04.2013 – 31.03.2016

Colorectal cancer (CRC) is the second most common deadly cancer in the United States. However, CRC screening can prevent CRC-related deaths. Options for screening include colonoscopy; during colonoscopy carcinoma precursors (adenomas) can be removed, preventing cancer development. However, the best way to conduct CRC screening is unknown, and insufficient clinical studies are available. Computer simulations of CRC development have been introduced to overcome these limitations. However, existing simulations are not publicly available and therefore have not been used to answer most of the practical questions. We therefore want to develop a detailed CRC simulation that we want to make available for general usage. In a second, complementary approach, we will develop a simple mathematical model and systematically add further details until accurate predictions can be made. We will calibrate our models to reflect CRC epidemiology and costs in Switzerland and the United States. In Switzerland, the introduction of a publicly funded CRC screening programme is currently under discussion; we will simulate costs and benefits of such a programme to inform the ongoing discussion. In addition, our model will be used to answer important questions for doctors and patients: We will address the best time point of screening colonoscopies, the best follow-up schedule after polyp detection, and the cost-effectiveness of various measures of quality assurance in colonoscopy.

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Mullis Primus | **Risk of cancer and long-term mortality in children treated with growth hormone: Swiss participation in the EU FP7 project "Safety and Appropriateness of Growth Hormone Treatment in Europe" (SAGhE)** (KLS 02948-02-2012)
Duration: 01.07.2012 – 31.12.2013

Recombinant human growth hormone (rhGH) was initially used to treat cases of primary severe growth hormone deficiency (GHD), but its uses have multiplied. GHD is the most common endocrine late effect after childhood cancer and/or cancer treatment. However, there are concerns about cancer risk and long-term mortality. Good long-term studies on the safety of rhGH replacement therapy are lacking. Switzerland is participating in a large European study that is investigating the long-term impact of GH therapy on adult height, quality of life, cancer incidence, and mortality.

Medical data will be collected from patient files in the hospitals. Information on quality of life and current health status will be assessed by questionnaires. To determine cancer incidence and mortality, we will compare this cohort to cantonal cancer registries and mortality statistics of the Swiss Federal Statistical Office. The results will aid adaptation of recommendations for treatment with rhGH in children to guarantee long-term safety for current and future patients. For former patients, preventive medical check-ups can be planned.

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Rohrmann Sabine | **Modifiable risk and protective factors of cancer – a population-based approach in Switzerland** (KFS 03048-08-2012)
Duration: 01.08.2013 – 30.07.2016

In Switzerland, cancer is a frequent cause of disease and death. A substantial proportion of cancer cases could be avoided. This study examines which factors are associated with cancer mortality. Of interest are not only established risk factors such as smoking, alcohol consumption, and obesity but also alternative and subjective determinants such as self-rated health. Moreover, sociocultural and environmental factors will be examined in relation to cancer. Another aim of this study is to develop a score that physicians can use to assess individual cancer prevention potential and that allows specific lifestyle recommendations.

This study is based on the Swiss National Cohort (SNC), which anonymously links data from the death registry with individual data from the censuses and health surveys. This opens the door to an abundance of sociodemographic and health-relevant information. This combined database will not only allow the calculation of survival time and mortality risk specifically for Switzerland but also derivation of a cancer risk score. The expected results will provide public health experts relevant information about single and combined risk factors, allowing them to plan and conduct prevention strategies more efficiently, and offer health services providers a basis for the assessment of individual cancer risk patterns.

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Spycher Ben D. | **The role of population mixing and exposure to infections in the aetiology of childhood leukaemia: a national cohort study**
(KFS 03049-08-2012)
Duration: 01.01.2013 – 31.12.2014

Leukaemia is the most important cancer in childhood, yet little is known about its causes. It has been suggested that leukaemia could be a complication of a common, yet unidentified infection. Epidemics of this infection – caused, for instance, by a rapid influx of people into a rural community – might thus lead to an increased incidence of leukaemia. Another hypothesis suggests that the shift of infections that used to occur in the first months and years of life to later years could increase the risk of leukaemia.

This project will examine both of these hypotheses. We will calculate measures of population influx and early exposure to infections for all children who lived in Switzerland between 1985 and 2012 using census data and other routine databases. Information on children who developed leukaemia during this time will be obtained from the Swiss National Childhood Cancer Registry (SCCR). Understanding the causes of leukaemia is crucial for preventing the disease. This project will help us to understand whether infections play a role. Only few previous studies were able to include the whole population of a country.

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