Cancer Research in Switzerland

A publication of the Cancer Research Switzerland foundation,
the Swiss Cancer League and the cantonal cancer leagues on their
funded research projects 2011
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Pia Zanetti's photographs are represented in public and private collections in Switzerland and abroad. Purchase of the Confederation Switzerland and the Swiss Foundation of Photography.

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Cancer Research in Switzerland

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Editorial

With total funding of 20 million Swiss francs, the Cancer Research Switzerland foundation (CRS), the Swiss Cancer League (SCL), and the cantonal and regional cancer leagues (CCL) invested a new record sum in academic cancer research in Switzerland in 2011. This was an increase of 10 per cent over the previous year and is the highest amount that the CRS, SCL, and CCL have ever awarded to oncology researchers in Switzerland. This is an achievement of which we can be proud.

In the research funding strategy of the partner organizations, the most important criterion is and will remain the quality of the projects funded. Based on experience with various funding instruments in past years, the boards of the partner organizations have decided to focus even more strongly on independent research projects in future. This funding is awarded to researchers following a rigorous selection procedure. This means that only the best and the most innovative projects are awarded grants.

Symbolic of that excellence are the photographs illustrating this report, which were taken during the latest tour of Circus Knie, the Swiss national Circus. Like the performances of the circus artists, the work of the researchers is the result of hard training, perseverance, precision, brilliant individual achievement, and good team work.

This fifth edition of the report Cancer Research in Switzerland presents the institutions and projects, both completed and approved, that were funded by the CRS, SCL, and CCL in 2011. The report is now being published each year, not every two years as in

Thomas Cerny

Jakob R. Passweg

the past, making the reporting on our research funding activities even more up-to-date. And for the first time, this reports presents in brief all projects and institutions that are funded by the CCL. This will give readers a comprehensive picture of research funding by the Cancer League as a whole association, which includes the SCL and the CCL.

We extend heartfelt thanks to all of the people who made these outstanding results possible through their charitable donations. Your generosity helps us to achieve continuous progress in oncology research and in the fight against cancer, so that persons with cancer will receive better treatment and care in the future. A big thank-you goes to all of the researchers for their extraordinary efforts in the service of cancer research. We also express our gratitude to all of the people who worked on this edition of the report.

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

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

Research funding: Outstanding research for patient benefit

In 2011 the Cancer Research Switzerland foundation (CRS) and the Swiss Cancer League (SCL) funded cancer research in Switzerland with a new record sum of CHF 16.7 million. A further CHF 3.3 million in research funding was provided by the cantonal and regional cancer leagues (CCL). This means that more money than ever before was given to oncology research in Switzerland – a result that was made possible by the contributions of the many charitable donors.

Cancer research in Switzerland is funded jointly by the CRS, SCL, and the CCL. The SCL and the CCL are engaged broadly in the fight against cancer – that is, through cancer prevention, research funding, and support and advising to persons with cancer and their family members. The CRS focuses exclusively on funding oncology research. The organizations share a common goal: to fund first-rate research at universities, hospitals, and academic research institutes to develop better treatments and thus to improve survival and quality of life in patients with cancer.

Cancer: A complex challenge

Each year there are about 37,000 new cases of cancer in Switzerland, and about 16,000 persons die of the disease. On average, one in three people in Switzerland will develop some form of cancer in their lifetime, and one in four will die of cancer. In all, cancer accounts for 29 % of all deaths among men and 22 % of all deaths among women. This makes cancer the second most common cause of death after cardiovascular diseases. In addition, cancer is not at all a disease of the elderly only. In fact, in the age group of 45 to 64 years, cancer is even the most frequent cause of death. No other disease destroys more productive years of peoples' lives than cancer. The number of new cases is expected to further rise in the future due to demographic changes alone.

Another challenge is the complexity of cancer. Cancer is a collective term for approximately 210 different diseases that differ greatly in cause, development, course, and treatment. And the more we learn about cancer, the more complex the picture that research uncovers is: Some types of cancer are now being subdivided into more and more specific subgroups. The individual tumour characteristics of a single subgroup vary considerably from patient to patient. And even the cancer cells in an individual tumour differ extensively at the cellular, genetic, and biochemical levels. In brief: The reality of the disease cancer appears to be much more complex than we assumed only some years ago. This makes research and innovation in oncology more important than ever today.

High-quality, patient-centred research

The research funding strategy of the boards of the CRS, SCL, and CCL focuses mainly on patient-centred research. This means that the organizations fund mainly research projects that aim to deliver findings that will possibly lead to direct benefits for patients – whether it be improvements in cancer prevention, early diagnosis, treatment success, or improved alleviation of consequences of the disease. Therefore, funding is granted for clinical research and for projects in psychosocial research, epidemiology, nursing sciences, prevention, public health, and health services research and outcome research

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

(research on the quality, effectiveness, and cost control of medical care). Another area given attention is basic research, which enlarges our understanding of how cancer develops and spreads and thus delivers a basis from which to develop new and better methods of diagnosis and treatment.

Quality thanks to professionalism and efficiency

Just as cancer is a complex disease, research on cancer is also a complicated and costly undertaking. To ensure that the highest quality research projects and the most important research organizations receive funding, the grant applications submitted by researchers are evaluated according to strict and clearly defined scientific criteria. Responsible for this review task is the Scientific Committee, a group of recognized experts with outstanding achievements in all areas relevant to cancer research. The Scientific Office is the competence centre and operational hub for research funding. The office organizes the call for and review of grant applications and handles budgetary and quality control of the supported research projects.

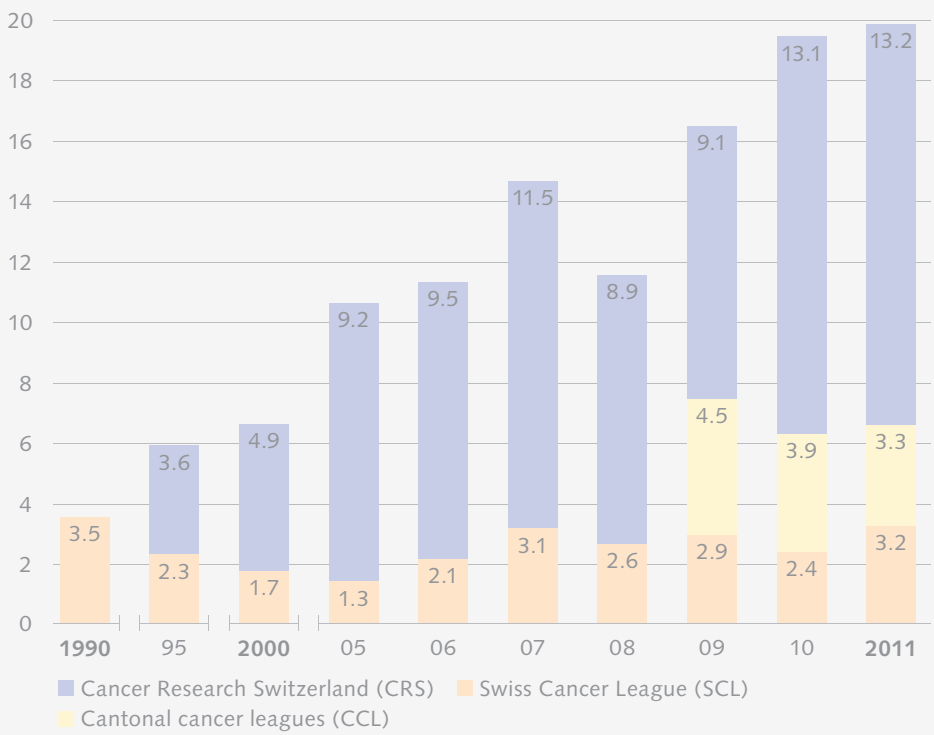
The Scientific Committee and the Scientific Office work for both the CRS and the SCL. Thanks to this combining of forces, research funding by the two partner organizations has for many years achieved a quality level that meets the highest international standards. At the same time, this use of synergies means that administrative costs are minimized and the charitable contributions are utilized efficiently, so that the greatest possible portion of the available monies can be put into the best research projects.

Record sum for research funding

In 2011 the CRS and the SCL together provided CHF 16.4 million for cancer research, a new record level of funding. A total of 76 research projects, bursaries, and research organizations were supported (Figure 1). Not included in these figures are contributions made to conferences, workshops, and international organizations. In addition to this, the CCL supported a total of 52 research projects and institutions, mainly in their cantons and regions, with a total of CHF 3.3 million in funding.

Figure 1

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



Including funding for other projects, total spending of the CRS and SCL on research funding was CHF 16.7 million in 2011 (Table 1). As in the two previous years, 80 % of the funds came from the CRS and 20 % from the SCL. Therefore, in 2011 the funding organizations contributed CHF 20 million to cancer research in Switzerland. On behalf of patients with cancer and also the researchers, we extend a big thank you to all of the generous donors who made this possible.

Distribution of cancer research spending

Similar to the reporting period 2009/2010, most of the funding – 84 % – went to independent research projects in 2011; 9 % went to Swiss research organizations as contributions for basic services; 5 % went to persons receiving bursaries; 2 % went to other projects, such as funds for scientific meetings, conferences, and workshops and contributions to international organizations like the EORTC Charitable Trust, the foundation for the European Organisation for Research and Treatment of Cancer. Thus the allocation of the research funding once again remained stable compared to previous years.

The funding for independent research projects increased by 18 %, from CHF 11.9 million in 2010 to CHF 14.1 million in 2011. About the same amount of funding as in the previous year went to persons receiving bursaries, and 20 % more funding than in 2010 went to research organizations in 2011. The funding for other projects remained constant.

Figure 2 shows the distribution of funds by the CRS and SCL to the cantons and the cantonal institutions. More than three-quarters of the funding for research projects, bursaries, and research prizes went to the university/university hospital cantons: Zurich, Lausanne, Bern, and Basel. Less than one-quarter of the funding was given to institutions in the cantons of Geneva, Aargau, St. Gallen, Ticino, and Fribourg.

Competition in independent research

At 84 % of the total funding in 2011, CHF 14.1 million was granted to independent research projects (Table 2). In the context of competition for limited research funds, this funding is granted to the best of the submitted grant applications. For this by far the

Table 1
Research funding by CRS and SCL in overview

Number of grant applications and amount applied for; number of grants and amounts granted in 2011 (all funding areas)

	Independent research projects	Bursaries	Research organizations	Other*	**Total**
CRS					
Number of grants approved	48	6	5	4	**63**
Amount granted (in kCHF)	10,942	750	1,510	163	**13,365**
Proportion of total funding (in %)	82 %	6 %	11 %	1 %	**100 %**
SCL					
Number of grants approved	15	1	0	21	**37**
Amount granted (in kCHF)	3,138	54	0	189	**3,381**
Proportion of total funding (in %)	93 %	2 %	0 %	5 %	**100 %**
Total CRS and SCL					
Number of grant applications	127	9	5	26	**167**
Number of grants approved	63	7	5	25	**100**
Amount applied for (in kCHF)	32,629	876	1,510	371	**35,386**
Amount granted (in kCHF)	14,080	804	1,510	352	**16,746**
Proportion of total funding (in %)	84 %	5 %	9 %	2 %	**100 %**

* Funding for scientific conferences, workshops, international organizations

most important area of research funding by the CRS and SCL, this was an increase of 27 % compared to the average of the record sums in the previous years 2009 and 2010. Compared to the period 2009/2010, 84 % in 2011 represents also an increase of 6 percentage points in the proportion of total funding going to independent research projects.

Of the 127 grant applications submitted, 63 projects were approved for funding. Of the amount of funding applied for, CHF 32.6 million, the board of the SCL and the foundation board of the CRS granted CHF 14.1 million. Relative to the number of grant applications, this is a grant approval success rate of not quite 50 % (average in 2009/2010: 33 %) and a monetary grant success rate of 43 % (average in 2009/2010: 27 %). This considerable improvement over the success rates in the period 2009/2010 was due primarily to two factors: For one, 14 % fewer grant applications were submitted in 2011 than in 2009/2010, and for another, 27 % more money was available to fund additional applications.

Positive development of the success rates

There was a welcome development concerning projects that the Scientific Committee deemed high quality after the review process and approved for funding but that the boards could not fund due to lack of monies. The number of these approved but not funded (ABNF) projects decreased from a total of 26 grant applications in 2010 to 15 in 2011. All of the ABNF projects in 2011 were in basic research, where the monetary grant success rate (amount applied for compared to amount granted) was 40 %.

Basic research thus continues to be the area with the highest amounts applied for and the highest amounts granted but also the area with the most competitive conditions. This is a consequence of the quota described below, the aim of which is to increase the funding of patient-centred research. A positive development in this connection is the improvement of the monetary grant success rate in basic research, which in 2010 was only 26 %. This is not least due to the increased efforts of the partner organizations in fund raising that targets companies or foundations, which allowed the partners to fund specific, quality-reviewed research projects using project and topic-specific donations.

In clinical research, which encompasses research studies with patients as well as laboratory research with human cells and tissues, the monetary grant success rate was 47 % (in 2010: 27 %). In psychosocial research the monetary grant success rate increased from only 8 % in 2010 to 48 % in 2011 and in epidemiological research from 52 % in 2010 to 57 % in 2011. Looking at the number of approved grant applications compared to number of submitted grant applications, we find the following grant success rates: 42 % for basic research, 54 % for clinical research, 60 % for psychosocial research, and 78 % for epidemiology.

Instruments to promote patient-centred research

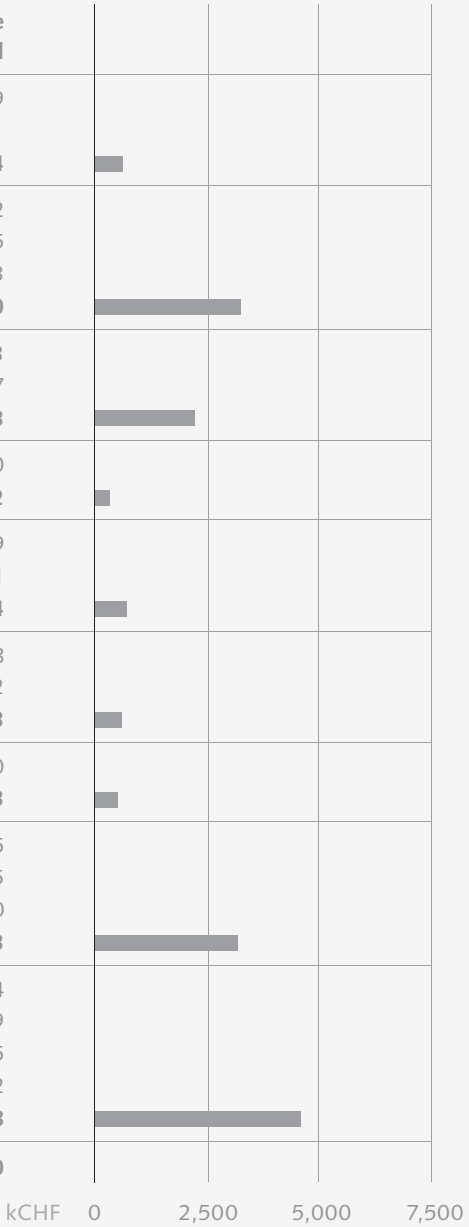
Patient-centred research is essential for continuous improvement of the medical and psychosocial care of patients with cancer. Central here is clinical research conducted independently of the pharmaceutical industry. For example, very important are research studies on treatment optimization, which aim to find the optimal combination and sequencing in time of existing treatment options, such as chemotherapy, immunotherapy, radiotherapy, and surgery, depending on type of cancer, stage of cancer, and the patient. Patient-centred research also includes psychosocial research, which focuses on the psychological and social consequences of cancer and aims to improve the quality of life of patients and also their family members. Epidemiological research studies the prevalence and incidence of cancers in the population and analyses the factors that affect cancer risk, such as age, sex, smoking, diet, exercise, social network, and environmental factors. Nursing research focuses on improving the care and support of patients with cancer and their families.

Quotas

To increase the funding of patient-centred research, various instruments were tried out and evaluated in recent years. Some measures did not produce the desired effect and were discontinued, but one instrument in particular – quotas – proved its worth. Within the area of independent research projects, 60 % of the funding is earmarked for patient-centred research. Two-thirds of that (or 40 % of the total

Figure 2
Distribution of cancer research funding to the cantons by CRS and SCL in 2011

Canton		Number of projects	Amount in kCHF	Percentage of total
AG	Cantonal Hospital, UAS, PSI	4	530	89
	Bursaries	1	67	11
	Total	**5**	**597**	**4**
BE	SAKK/IBCSG/SPOG/SCCR	12	1,050	32
	University/University Hospital	7	1,440	45
	Bursaries and awards	5	741	23
	Total	**24**	**3,231**	**20**
BL-BS	FMI	3	487	23
	University/University Hospital	10	1,676	77
	Total	**13**	**2,163**	**13**
FR	University	1	311	100
	Total	**1**	**311**	**2**
GE	University/University Hospital	5	674	99
	Bursaries	1	5	1
	Total	**6**	**679**	**4**
SG	Cantonal Hospital	5	449	78
	Bursaries	1	128	22
	Total	**6**	**577**	**3**
TI	Hospitals/IOSI	3	481	100
	Total	**3**	**481**	**3**
VD	EPFL	6	1,275	35
	University/CHUV	11	2,374	65
	Bursaries	1	14	0
	Total	**18**	**3,663**	**23**
ZH	NICER	1	200	4
	ETHZ	4	864	19
	University/University Hospital	20	3,404	75
	Bursaries and awards	2	65	2
	Total	**27**	**4,533**	**28**
	Total	**103**	**16,235**	**100**

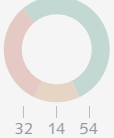


Abbreviations

AG UAS = University of Applied Sciences
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
BL-BS FMI = Friedrich Miescher Institute
TI IOSI = Oncology Institute of Southern Switzerland
VD EPFL = Swiss Federal Institute of Technology Lausanne
CHUV = University Hospital Lausanne
ZH NICER = National Institute for Cancer Epidemiology and Registration
ETHZ = Swiss Federal Institute of Technology Zurich

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

		2010	2011	Change compared to prior year
Basic biomedical research				
Number of grant applications		88	69	**–22 %**
Amount applied for	(in kCHF)	26,611	19,061	**–28 %**
	(in %)	59 %	58 %	**–1 %**
Number of grants approved		29	29	**0 %**
Amount granted	(in kCHF)	6,998	7,559	**8 %**
	(in %)	59 %	54 %	**–5 %**
Clinical research				
Number of grant applications		46	39	**–15 %**
Amount applied for	(in kCHF)	11,450	9,793	**–14 %**
	(in %)	25 %	30 %	**5 %**
Number of grants approved		15	21	**40 %**
Amount granted	(in kCHF)	3,139	4,556	**45 %**
	(in %)	26 %	32 %	**6 %**
Psychosocial research				
Number of grant applications		14	10	**–29 %**
Amount applied for	(in kCHF)	4,298	1,953	**–55 %**
	(in %)	10 %	6 %	**–4 %**
Number of grants approved		4	6	**50 %**
Amount granted	(in kCHF)	364	931	**156 %**
	(in %)	3 %	7 %	**4 %**
Epidemiological research				
Number of grant applications		8	9	**13 %**
Amount applied for	(in kCHF)	2,711	1,822	**–33 %**
	(in %)	6 %	6 %	**0 %**
Number of grants approved		5	7	**40 %**
Amount granted	(in kCHF)	1,398	1,034	**–26 %**
	(in %)	12 %	7 %	**–5 %**
All projects				
Number of grant applications		156	127	**–19 %**
Amount applied for	(in kCHF)	45,070	32,629	**–28 %**
Number of grants approved		53	63	**19 %**
Amount granted	(in kCHF)	11,899	14,080	**18 %**



(in %)

funds for independent research projects) are reserved for clinical research and one-third (or 20 % of the total funds) for research in the psychosocial area, nursing sciences, epidemiology, prevention, public health, health services research and outcomes research. The remaining 40 % of funding for independent research projects goes to basic research.

In 2011, 46 % of the funds for independent research projects went to patient-centred research – that is, to clinical, psychosocial, and epidemiological research (Table 3). Compared to the prior year, this was an increase of 5 percentage points; 54 % of the funds for independent research projects went to basic research (in 2010: 59 %). Since 2004, this distribution has remained quite stable, with average values of 47 % going to patient-centred research and 53 % to basic research. The main reason why this instrument has not achieved yet the quota of 60 % for patient-centred research is that too few grant applications meeting the high standards of quality are submitted in these research disciplines. And for the CRS and the SCL, the most heavily weighted criterion in the decision to grant funding continues to be the criterion of highest quality research.

Research organizations

Since 2009 the CRS has supported important and established Swiss cancer research organizations by providing funds for basic services that these organizations perform for the benefit of patient-centred research in Switzerland. Clinical research is very costly and complex per se, and it would bring many hospitals to the limits of their financial and human resources if they received no support. For this reason, the services provided by research organizations that do a large part of the work associated with the actual clinical research are of inestimable value for clinical cancer research in Switzerland. The tasks include, for example, designing study protocols; coordinating multicentre and international studies; administrative tasks for the study approval process with Swissmedic and the ethics committees; and collecting, managing, and analysing data for cancer registration and epidemiology. These basic services are now funded based on performance agreements that link the annual funding to clear targets and reporting duties. Through these structural contributions, the aim is to reward and ensure the work of the research organizations in the longer term, whereby the existence of the organizations must not be dependent on these funds.

Table 3
Distribution of funds by CRS and SCL for independent research projects by research area and year

	2003	2004	2005	2006	2007	2008	2009	2010	2011
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
in %	65 %	56 %	49 %	52 %	56 %	48 %	47 %	59 %	54 %
Clinical research									
Total in million CHF	2.19	3.31	3.36	3.31	3.85	2.90	3.96	3.14	4.56
in %	30 %	31 %	40 %	34 %	35 %	32 %	39 %	26 %	32 %
Psychosocial research									
Total in million CHF	0.14	1.00	0.61	0.74	1.05	0.84	0.70	0.36	0.93
in %	2 %	9 %	7 %	7 %	9 %	9 %	7 %	3 %	7 %
Epidemiological research									
Total in million CHF	0.22	0.37	0.31	0.74	0.00	0.93	0.74	1.40	1.03
in %	3 %	4 %	4 %	7 %	0 %	11%	7 %	12 %	7 %
All projects									
Total in million CHF	7.30	10.68	8.46	9.93	11.02	9.02	10.20	11.90	14.08

The following organizations were supported by the CRS in 2011:

- Swiss Group for Clinical Cancer Research (SAKK): CHF 600,000
  SAKK is a non-profit organization that has initiated and coordinated clinical studies on cancer treatment in Switzerland and internationally since 1965. SAKK encompasses a wide network of about 20 Swiss research groups and a coordination centre in Bern.
- International Breast Cancer Study Group (IBCSG): CHF 560,000
  Since 1977 the IBCSG has conducted academic clinical trials with the aim to improve the treatment of women with breast cancer.
- National Institute for Cancer Epidemiology and Registration (NICER): CHF 200,000
  The NICER foundation promotes and supports population-based cancer registration and epidemiological cancer research in Switzerland.
- Swiss Paediatric Oncology Group (SPOG): CHF 100,000
  The SPOG supports clinical cancer research in the area of paediatric oncology, in particular in the framework of cooperative national studies.
- Swiss Childhood Cancer Registry (SCCR): CHF 50,000
  The SCCR is a national, population-based cancer registry for children. It collects data on new cancer diagnoses and documents treatment and long-term follow-up.

For this instrument CRS reserves a maximum of CHF two million, or maximum 20 % of the total annual research funding budget, per year. These monies are distributed explicitly *not* according to the "watering can" principle but instead to only five to maximal seven important and long-established research organizations.

Research funding by the cantonal cancer leagues

In addition to research funding by the CRS and SCL, the CCL also supported a number of research projects and institutions in 2011 – mainly in their cantons (Table 4). The figures reported here include not only funding for research projects in the narrow sense but also support given to institutions such as the cantonal cancer registries, which provide services that make cancer research possible or conduct their own research studies. In part the cantonal cancer leagues also supported research projects that the SCL and CRS reviewed and approved for funding but did not fund in full.

In total, 11 cantonal cancer leagues gave CHF 3.3 million to 52 research projects and institutions in 2011. Compared to 2010, that was five projects fewer and 21 % less funding. Two-thirds of the monies were from the cantonal cancer leagues of Geneva, Zurich, and Bern; the remaining one-third was from the cantonal cancer leagues of Ticino, Aargau, Basel, Central Switzerland, Neuchâtel, Vaud, and Grisons. The three cantonal cancer leagues of Eastern Switzerland, Schaffhausen, and Thurgau, which provided funding for research in 2010, did not fund research in 2011. At the same time, the cantonal cancer leagues of Central Switzerland and Vaud provided funds for research in 2011, after having not funded research in 2010. Detailed information on research funding by the cantonal cancer leagues in 2011 is presented beginning on page 32.

Overview of the research funding in 2011

In all, together the CRS, SCL, and the CCL supported a total of 152 research projects, bursaries, research organizations and institutions, and other projects in 2011 (Table 5). They provided a total of CHF 20 million to fund oncology research in Switzerland. This is a 10 % increase in total funding over the prior year and is the highest sum that the CRS, SCL, and the CCL together have ever provided to support cancer research in Switzerland. We extend sincere thanks to the many donors who made this record result possible.

Table 4
Research funding by the cantonal cancer leagues in overview

Number of projects and institutions supported and amount granted in 2011 compared to average amount in prior years 2009/2010

Cantonal cancer leagues	Number of projects and institutions supported 2009/2010 Ø per year	Number of projects and institutions supported 2011	Change compared to average in 2009/2010 (absolute)	Amount granted 2009/2010 Ø per year in kCHF	Amount granted 2011 in kCHF	Change compared to average in 2009/2010 (relative)
Aargau	2	3	1	167.7	279.5	67 %
Basel	12	7	–5	769.6	270.0	–65 %
Bern	8	8	0	460.0	500.1	9 %
Geneva	8	11	3	992.1	944.0	–5 %
Grisons	2	1	–1	32.5	5.0	–85 %
Neuchâtel	1	1	0	174.5	124.9	–28 %
Eastern Switzerland*	2	0	–2	294.2	0.0	–
Schaffhausen	2	0	–2	25.0	0.0	–
Ticino	5	6	1	270.8	290.0	7 %
Thurgau	1	0	–1	12.5	0.0	–
Vaud	0	1	1	0.0	19.4	–
Central Switzerland	0	2	2	0.0	133.0	–
Zurich	14	12	–2	988.4	728.4	–26 %
Total	**57**	**52**	**–5**	**4,187.3**	**3,294.3**	**–21 %**

* In 2011 the cancer leagues of St. Gallen-Appenzell and Glarus merged to become the Eastern Switzerland Cancer League.

Dr. 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 Cancer Research Switzerland foundation. One of the focuses of his work is the implementation of the National Cancer Programme for Switzerland 2011–2015.
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Table 5
Research funding by CRS, SCL, and the CCL in overview

Number of grants approved and amount granted in 2011 and change compared to prior year 2010 (all funding areas)

	Independent research projects		Bursaries		Research organizations		Other*		**Total**	
CRS										
Number of grants approved	48	14 %	6	20 %	5	67 %	4	0 %	**63**	13 %
Amount granted (in kCHF)	10,942	14 %	750	7 %	1,510	20 %	163	2 %	**13,365**	14 %
SCL										
Number of grants approved	15	36 %	1	–67 %	–	–	21	11 %	**37**	12 %
Amount granted (in kCHF)	3,138	36 %	54	–56 %	–	–	189	–1 %	**3,381**	29 %
CCL										
Number of grants approved	52	–7 %	–	–	–	–	–	–	**52**	–7 %
Amount granted (in kCHF)	3,294	–15 %	–	–	–	–	–	–	**3,294**	–15 %
Total CRS, SCL, and CCL										
Number of grants approved	115	6 %	7	–13 %	5	67 %	25	9 %	**152**	5 %
Amount granted (in kCHF)	17,374	10 %	804	–3 %	1,510	20 %	352	0 %	**20,040**	10 %

Change compared to 2010

* Funding for scientific conferences, workshops, and international organizations

(in %)

Partner organizations and committees

Cancer Research Switzerland foundation (CRS)

In existence since 1990, the Cancer Research Switzerland foundation generates donations that help provide funding for all areas of cancer research: basic research, clinical, epidemiological, psychosocial research, and paediatric research (research on childhood cancer). The CRS foundation board 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 is made up of experts in cancer research and reviews the research proposals submitted according to clearly defined guidelines. The CRS also supports the development and implementation of measures to fight cancer in Switzerland – namely, the National Cancer Programme 2011–2015.

Contact information

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www.cancerresearch.ch

Swiss Cancer League (SCL)

The Swiss Cancer League is a charitable, private non-profit organization. Its work is dedicated 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 aid to persons with cancer and their families in all phases of the disease and in dying. It funds cancer research, sensitizes the public to prevention measures, advocates for early diagnosis and treatment, provides advice to persons with cancer and their loved ones, and offers social support. The 19 cantonal cancer leagues are active at the local and regional levels. They provide psychosocial advice and financial support to persons with cancer and their families locally. Most of the funding for the SCL's numerous tasks comes from donations. The SCL funds cancer research, with a special focus on supporting patient-centred research projects.

Contact information

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www.swisscancer.ch

Kurt Bodenmüller
Communications manager of the Scientific Office, Swiss Cancer League

Cantonal cancer leagues (CCL)

In the 19 cantonal and regional cancer leagues, persons with cancer and their family members receive personal, individual advice from experts on treatment and on financial and organizational questions. The personnel 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 situation. They provide contacts to other support institutions, such as home care organizations. If persons with cancer come into financial difficulties due to their illness, they can apply for support payments. The CCL organize group meetings and courses, where persons affected by cancer can talk about their fears and experiences and learn to deal with their illness. Some cancer leagues offer specialized psycho-oncology support for children of adults with cancer. In some cantons, there are outpatient oncology care services that support persons with cancer at home.

The CCL are active in Switzerland and in Liechtenstein. Not every CCL offers the same services. The extent and type of services available depend strongly on the financial and human resources of the CCL as well as on the services offered 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 Cancer Research Switzerland foundation (CRS)

The board of the Cancer Research Switzerland foundation is made up of one representative 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 in the different research areas; and further, independent persons. Prof. Thomas Cerny, MD, has been president of the foundation since 2009, and Prof. Richard Herrmann, MD, is vice-president.

The eight members of the CRS board are:

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

Eduard Holdener, MD
Therwil
Independent person
since 2009

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

Isabel Lechtman-Mortara
Geneva
Independent person
since 2009

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

Gallus Mayer
Banking specialist
Head of Asset & Liability Management
Notenstein Private Bank Ltd
St. Gallen
Treasurer
since 2009

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

PD Nicolas von der Weid, MD
Head of Oncology/Haematology
Co-head 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 (SCL)

In April 2010 Prof. Jakob R. Passweg, MD, was elected president of the Swiss Cancer League. Gilbert Bernard Zulian, MD, is vice-president.

The ten members of the SCL board are:

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

Lucienne Bigler-Perrotin
Manager
Geneva Cancer League
since 2009

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

Gallus Mayer
Banking specialist
Head of Asset & Liability Management
Notenstein Private Bank Ltd
St. Gallen
Treasurer
since 2009

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

Hans Neuenschwander, MD
Medical director of Palliative Care
Regional Hospital of Lugano
since 2010

Irène Bachmann-Mettler
Project head of 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
Fribourg Cantonal Hospital
since 2006

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

The Scientific Committee

The Scientific Committee is responsible for evaluating the research grant applications submitted to the Cancer Research Switzerland foundation (CRS) 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. Each member of the committee handles on average nearly 20 grant applications per year. More than half of the proposals are in basic research.

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

As the financial means are limited, it is never possible to approve grants for all proposals that the committee judges to be of good quality and worthy of funding. In the reporting period 2011 there were 15 research proposals that could not be approved for funding despite their excellent quality. In total the Scientific Committee reviewed 127 grant applications.

Operational support for the Scientific Committee's important tasks and responsibility is provided by the Scientific Office of the SCL and the CRS. It organizes the call for and the review of proposals and is responsible for quality control of the supported 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 research proposal 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 proposal.

↓

The reviewers evaluate the proposal. Four to six reviews are obtained for each research proposal, two of which are by Scientific Committee members.

↓

The Scientific Office collects the reviews and puts them in a file.

↓

The research proposal 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 proposals ranked according to the committee's recommendations.

↓

The ranking list is forwarded to the boards of the Cancer Research Switzerland foundation and the Swiss Cancer League, which then decide which proposals 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

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

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

Ellen Benhamou, MD
Gustave Roussy Cancer Institute
Villejuif Cedex, France
2003–2011

Prof. Holger Moch, MD
Institute of Surgical Pathology
University Hospital Zurich
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
University Children's Hospital Zurich
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
University Hospital Bern
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
University Hospital Zurich
Zurich, Switzerland
since 2010

Prof. Kurt Fritzsche, MD
Department of Psychosomatic
Medicine and Psychotherapy
University Hospital
Freiburg, 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

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
since 2000

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

Research awards: Honouring outstanding cancer researchers

The Swiss Cancer League (SCL) regularly gives awards for excellent research or for committed promotion of research activities in the areas of the prevention and early detection of cancer and the fight against cancer. In addition, each year the Scientific Office organizes the call for grant applications and the evaluation of the submitted research proposals for the SWISS BRIDGE AWARD.

The Robert Wenner Award of the SCL has been awarded regularly to cancer researchers under the age of 45 for outstanding research results and well-received research papers since 1983. This award was endowed by Robert Wenner, a gynaecologist from Basel who died in 1979. The award winners receive CHF 100,000, with CHF 80,000 earmarked for an ongoing project and CHF 20,000 as discretionary funds. For the researchers, this recognition means both honour for their previous achievements and incentive for future research efforts. As the greater 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. In 2001 the Robert Wenner Award was given to two researchers.

Research at the intersection of clinical medicine, epidemiology, and public health

The first Robert Wenner Award 2011 was awarded to physician and epidemiologist Julia Bohlius. Bohlius has been conducting research at the interface of oncology/haematology, epidemiology, and public

The Cancer Prize of the Swiss Cancer League 2011

Since 1960 the Swiss Cancer League has awarded the Cancer Prize recognizing persons who have made excellent contributions to cancer research or who have shown 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 it goals. The prize of CHF 10,000 is usually awarded each year.

The Cancer Prize 2011 was awarded to Prof. Urs Metzger, MD and Dr. h.c., for his committed work as president of the Swiss Cancer League from 1995 to 1998, his work as an expert in the area of colon cancer prevention, and his services in research on and surgical treatment of colon cancer.

As chief physician of the surgery clinic and medical director of Triemli Municipal and Central Hospital in Zurich (until 2010), Metzger's particular focus was the pathogenesis, prevention, and surgical treatment of colorectal cancer. He has been an honorary member of the Swiss Cancer League, for which he served as president from 1995 to 1998, since 2001. As a member of the expert group on colon cancer prevention, he played a substantial role in developing the "Colorectal Cancer Programme", which demands systematic early detection of colon cancer in the Swiss population aged 50 to 69. At the end of April 2011, the Swiss Cancer League lodged an application with the Federal Office of Public Health (FOPH) for coverage of the costs of the programme by the mandatory health insurance. One of Metzger's greatest concerns was and still is the provision of sound and understandable information to patients and their family members – whether in personal meetings with patients or through lectures, discussions, or brochures.

www.krebsliga.ch/krebspreis

health for about 10 years. Since 2007, the 41-year-old has been a research fellow at the Institute of Social and Preventive Medicine (ISPM) at the University of Bern, where she heads the Cancer Research Group. Her fields of work are systematic reviews of studies in clinical cancer research and meta-analyses of large data sets with clinical data on individual patients to assess treatment effectiveness in cancer patients.

One of Bohlius' most significant achievements to date is her years of research on the effect of erythropoiesis-stimulating agents to reduce anaemia on the survival of patients with cancer. In a paper published in the renowned journal *The Lancet* in 2009, she showed that these drugs – contrary to earlier assumptions – increased mortality in cancer patients. As a result, the official treatment recommendations were changed and treatment with these drugs was further restricted in patients with cancer. In the future, Bohlius plans to focus more on the identification of risk factors, so that cancers can be either prevented or detected earlier and cancer treatment improved. Here her focus is on tumour diseases in persons who are HIV positive in Europe, America, and southern Africa.

Research from the laboratory to the clinic – and back

Just how successful research at the interface between the laboratory and the clinic can be is shown by the second winner of the Robert Wenner Prize 2011, Adrian Ochsenbein. Ochsenbein is chief physician at the Institute of Medical Oncology of Bern University Hospital and head of the Tumour Immunology Research Group in the Department of Clinical Research at the University of Bern. His main research interest is immunosurveillance, surveillance of tumours by

Julia Bohlius, MD, MScPH

Julia Bohlius was born in Tettnang in southern Germany in 1971. After completing medical studies at the University of Hamburg and practicums and internships in Columbia, China, the United States, and Germany, she completed her MD at the University of Cologne in 2002, with a systematic review on the treatment of lymphomas. Two years later she completed a Master of Science in Public Health at the London School of Hygiene and Tropical Medicine. Returning to Cologne, she worked as a medical resident and research fellow at the Department for Haematology, Oncology and Infectious Disease at the University of Cologne and was at the same time a research associate in the Cochrane Haematological Malignancies Group. Bohlius came to Switzerland in 2007, where she became head of the Cancer Research Group at the Institute of Social and Preventive Medicine (ISPM) at the University of Bern. In August 2011 she won a Swiss National Science Foundation research grant (Ambizione-SCORE programme). Bohlius lives with her family in Seeland.

Prof. Adrian Ochsenbein, MD

Adrian Ochsenbein was born in Derendingen, Solothurn, in 1967. After completing medical studies at the University of Bern, he began his research activity at the Institute of Experimental Immunology at University Hospital Zurich in 1996 under the direction of Nobel Laureate Prof. Rolf Zinkernagel and Prof. Hans Hengartner. In 2001 he completed a Habilitation on the mechanisms of the immune response. After a year of postdoctoral research in Seattle, Washington, he was named assistant professor in 2003 and extraordinary professor (Extraordinarius) in 2010 in the Medical Faculty of the University of Bern. Today Ochsenbein is head of the Tumour Immunology Research Group in the Department of Clinical Research at the University of Bern, and he is also chief physician at the Institute of Medical Oncology, Bern University Hospital. He heads the External Oncology Service of the canton of Bern. Ochsenbein is married and has two sons.

the immune system. To study the mechanisms of immunosurveillance, he and his research group work primarily with tumour mice models. In parallel, in the context of clinical studies with patients, he studies how the findings from the laboratory can be translated into new strategies for cancer immunotherapy.

In a highly regarded paper published in the renowned journal *Nature* in 2001, Ochsenbein showed that tumours that stay outside secondary lymphatic organs can remain largely undisturbed by the immune system. The reason is that the presentation of tumour antigens to the immune cells – which normally produces an immune response – is relatively inefficient in cancer cells. Subsequently, thanks to a professorship of the Swiss National Science Foundation (SNSF), he was able to set up his own laboratory at the University of Bern. Here he studies the specific molecular and cellular processes that result in the immune system ignoring cancer cells or even promoting their growth instead of destroying them. Ochsenbein focuses in his research on blood cancers such as myeloid leukaemia.

www.krebsliga.ch/rwp

Kurt Bodenmüller
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 since 2008.
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SWISS BRIDGE AWARD 2011

SWISS BRIDGE was established upon the initiative of Thomas Hoepli, who was formerly managing director of the foundation and today is a member of the foundation board. The purpose of the foundation, which was set up in 1997 with the support of the Swiss Cancer League, is to support high-quality research projects in Switzerland and abroad in the fight against cancer using funds that come from private donors and foundations, such as the Stammbach Foundation in Basel. SWISS BRIDGE has a foundation board, an international scientific committee, a board of patrons, and a loyal circle of supporters and friends.

Starting in 2000, each year the foundation has given the SWISS BRIDGE AWARD, totalling CHF 500,000. The award honours researchers whose research work promises to achieve milestones in the study of and in the fight against cancer. The Scientific Office of the Swiss Cancer League organizes the call for research grant applications and the review of the projects submitted for the award. Up to now, the SWISS BRIDGE AWARD has awarded a total of CHF 6.85 million for projects conducted by researchers in Belgium, England, France, Israel, Italy, Norway, Sweden, Spain, and Switzerland.

The recipients of the SWISS BRIDGE AWARD in 2011 were:
Prof. Jürg Schwaller, MD Department of Biomedicine, University Hospital Basel (CHF 175,000)
Prof. Shai Izraeli, MD Department of Pediatric Hemato-Oncology and Cancer Research Center, Sheba Medical Center, Tel Hashomer, Israel (CHF 150,000)
Prof. Monika Hegi, PhD Director of the Laboratory of Brain Tumor Biology and Genetics, Department of Clinical Neurosciences, University Hospital Lausanne (CHUV) (CHF 175,000)

www.swissbridge.ch

National Cancer Programme 2011–2015

Status of implementation in research and therapy

In April 2011 Oncosuisse launched the National Cancer Programme (NCP) for the period 2011–2015; it was worked out together with the Swiss cancer organizations and with the support of the federal government and the cantons. The NCP report defines over 100 specific measures in 10 priority areas that aim at improving the fight against cancer and making it more efficient. In the following interview, Prof. Richard Herrmann, MD, president of Oncosuisse, explains where the NCP stands in research and therapy.

The NCP 2011–2015 has been underway for a year and a half now. Where do we stand?
We have clear expectations concerning implementation of the NCP. We have hired a programme head to coordinate the different areas. And we have defined goals that we want to achieve. The focus of the work in the first year was on creating suitable framework conditions for implementing the goals. For this, we built platforms for four priority areas: provisions (prevention and early diagnosis), support (treatment, care, and psycho-oncology), aftercare (psychosocial support, rehabilitation, and palliative care), and research (including epidemiology and monitoring). The head of each platform is responsible for initiating activities for achieving the goals of the NCP.

Isn't the development of a cancer programme also a way to build a community, to integrate partners?
That is surely so. I see the advantage of developing a programme like this first of all in the fact that the actors involved are forced to think about their goals, put them on paper, and communicate them. Everybody then knows what the others are aiming to achieve, and parties can get together to achieve something jointly. The working out of a programme is just the first step, however. We have to bring the different actors together regularly and actively. For this reason, we organize an annual cancer reporting, at which all persons involved and interested can participate, for a joint assessment of the situation.

One of the priorities is cancer research. What are the goals of the NCP in research?
A central goal is the promotion of translational research. This concerns the way from preclinical research, basic research in the laboratory, to the clinic, for applications with people. A second important goal is to improve the conditions for clinical cancer research. Clinical cancer research – and clinical research in general – suffers in Switzerland because of the enormous burden of regulation. The costs associated with this are very high, and it leads to numerous restrictions for clinical cancer research. The over-regulation is also a reason why many people decide not to go into research at all.

Prof. Richard Herrmann, MD
President of Oncosuisse and head of the Departement of Clinical Research, University Hospital Basel

In the fall of 2011 the Swiss Parliament passed the new Swiss law on research involving humans (Humanforschungsgesetz, HFG). When developing the law, Oncosuisse and other organizations worked together towards improving the conditions for clinical research through the law. How successful were they?

As soon as the HFG and the ordinances come into force, it should be easier overall for us to conduct clinical research. The main thing is that the law regulates better what tasks are whose responsibility, so that the different decision-making committees – Swissmedic and the ethics committees – are not always having to monitor each other. We hope that this will simplify the procedures.

Among other things, the NCP seeks to increase health services research and outcomes research. What are they about?

A central concern of the NCP is to see that persons with cancer receive the best possible care all over Switzerland. However, we know that there are geographical differences in the quality of health care services. Health services research examines what differences exist, why they persist, and – in regions where health services are not optimal – how services can be improved. Outcomes research is about having the persons working in clinical research or in the medical care of persons with cancer regularly report on what they have achieved. We cannot simply assert that we are getting better. We also have to demonstrate that we have in fact become better, that treatment results have improved, for instance, that patients are doing better, or that the number of cancer cases has gone down.

Thanks to predictive markers, patients with the same cancer are being subdivided into more and more subgroups. What is the significance of the development of personalized medicine for cancer research?

Personalized medicine indeed results in a subdivision of cancers into many subgroups. This also means that the prevailing treatment standards have to be re-examined. If the course of a disease is so different that two or more subgroups exist, the standards may have to be refined and adapted depending on the subgroup. And that is a task for clinical research. But with this research there are additional challenges, because the number of patients per subgroup is small, possibly too small. To have a sufficiently large number of patients to produce verifiable conclusions, studies of this kind increasingly have to be conducted at the international level.

More and more types of cancer are thus becoming rare cancers. The NCP also seeks to be active in this area, to which also paediatric oncology belongs. How?

The rare diseases are not only addressed by the NCP. Not only in oncology but in other areas as well they are held today to be an important topic with a need for action. The Federal Office of Public Health (FOPH) has put together a working group to study how the problem should be approached. One example is an approval process of new drugs for rare diseases for which the requirements should not be as stringent as those for approval of drugs for common diseases.

What are the goals of the NCP in the area of cancer treatment?

It is internationally recognized today that cancer treatment is a multidisciplinary task. To assess a cancer and to decide what care and treatment are needed in a specific situation, different specialists must always be involved. The NCP demands that all patients have the right to have their cases discussed by an interdisciplinary tumour board. A further point is that standards for diagnostic and therapeutic measures that are binding for physicians and nurses must be defined at the national level. Of course, there always has to be some leeway for the individual treatment of a patient, if certain situations demand a well-founded deviation from the standard.

What body/committee should establish treatment standards?

It has to be specialists and not health insurance companies, for example. A national organization that defines these standards would be ideal. To this purpose we are having talks with the Swiss Society of Medical Oncology (SGMO). But other professional associations must also be involved in the process. At the international level there are standards that set the frame within which one can move, but these

standards have to be adapted to conditions in Switzerland, as certain European standards are very vaguely worded or contain adaptations to countries that are at a much lower level economically compared to Switzerland.

Should the standards also be binding for coverage of a treatment by the health insurance companies? Approximately 60 per cent of cancer drugs are used off-label, which means used in a way that is different (different situation or indication) from that described in the approved drug label.

That is indeed a delicate topic. The health insurance companies reimburse the cost of those drugs that are approved, registered, and on the list of pharmaceutical specialities. But these cases cover only about 40 per cent of the real world. Many deviations from this rule are in fact accepted by the insurers, but their decisions have no legal basis. Oncosuisse is currently having talks with the FOPH, Swissmedic, and the State Secretariat for Education and Research (SER). The goal of the discussions is to set up rules that give a larger proportion of the cancer treatments a legal foundation than is the case up to now.

The guidelines would have to be changed continuously to keep up with medical advances. But is it not so that both the FOPH and Swissmedic lag greatly behind the rapid development?

That is correct. A standard that according to international consensus is found to be right is not static but dynamic. This means that guidelines can change from year to year or every few years owing to new findings or new medications. But the legal regulations state that a health insurance company must only pay for drugs that are approved, registered, and on the list of pharmaceutical specialities. Anything else is actually illegal from a legal standpoint. If I as physician do not treat a patient as described in the defined standard, the patient can sue me. And the patient would probably win in court, even if I had

obeyed the law. This is because I must treat a patient off-label – that is, according to the latest state-of-the-art science. If I were to take proceedings against the FOPH, Swissmedic, or the health insurance company, I would probably win in court. It is a constant weighing up of what the law foresees and what is best for the patient.

The NCP wants to see all patients receive the best possible care. But for rare cancers, that is certainly only possible at specialized centres. Has any progress been made in this regard?

For me it is a question of initiative and organization. I am firmly convinced that the majority of Swiss oncologists would welcome national competence centres for rare cancers, with which they would have to arrange procedure and treatment of a patient. The goal cannot be to have all patients cared for at a centre of this kind on a long-term basis. Instead, the patient's treatment would be coordinated with the centre; in addition, research projects would be organized from the centres. This development will take time, however. And I believe that incentives from the national side are also needed for centres of this kind to be established. Our decentralized health care system, for which the cantons are responsible, tends to hinder these endeavours.

Are the federal government and the cantons willing to work together to find solutions?

Yes, definitely. The Dialog Nationale Gesundheitspolitik (national health policy dialogue), the permanent platform of the federal government and the cantons, is currently working on the implementation of the goals of the NCP at the policy level. Thanks to this platform, we should also have the support of the cantons. The goal is to get representatives of the administration and policy to stand behind our ideas as soon as possible.

For the NCP, what would you like to see from the Cancer Research Switzerland (CRS) and the Swiss Cancer League (SCL)?

As members of Oncosuisse, the SCL and the CRS are two very important sponsors of the NCP. The SCL stands out with long years of experience in many areas covered by the NCP. Many key persons at the SCL are important actors in the NCP. I am very glad we maintain such close cooperation, for without the competence and experience of the SCL, the NCP

National Cancer Programme for Switzerland 2011–2015

The fight against cancer is a complex, multidisciplinary task that requires the coordination of many actors. To this purpose, the Swiss cancer organizations, with the support of the federal government and the cantons, have worked out the National Cancer Programme 2011–2015 (NCP).

The NCP 2011–2015 defines 10 areas of priority with specific measures to be followed within each. The programme has chosen an approach that transcends the individual disciplines, for only a complete chain of measures – from prevention to early diagnosis to therapy to rehabilitation or palliative care – has the chance of achieving effective improvements in the fight against cancer. There are three main goals: Every person living in Switzerland should be equally entitled to the lowest possible cancer risk through prevention and early diagnosis, to appropriate diagnostics and treatment according to the latest findings and psychosocial and – where needed – palliative care in the case of illness. The programme aims to improve quality and to close gaps in services and care.

The NCP 2011–2015 presents specific recommendations for the fight against cancer. It is directed at policy decision-makers at federal and cantonal levels, organizations in the health care system, researchers and decision-makers in hospitals and universities, and also the public. The report presents an overview of the actions and ensures transparency for all actors.

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could not function. As for the CRS, we hope that – in addition to its generous financing of organization and infrastructure – it will also fund research programmes, especially in the area of translational research.

How does the National Cancer Programme for Switzerland differ from cancer programmes in other countries?

The NCP relies heavily on the commitment of the persons involved, who mostly serve according to the "militia system" (they serve while being in employment elsewhere) and without compensation, because there are no budgeted funds available. Naturally, there are structures according to which the whole programme is coordinated. But the basic plan, the ideas, and the work come from the grassroots. In this way, the NCP for Switzerland differs from comparable cancer programmes, such as those in France or Germany, where the programme comes from the ministers and has funds available for programme implementation. The advantage of our NCP is that with the activities of the supporters at the basis, people have a stronger feeling that they can achieve something themselves than is the case when a programme is decreed from the top down.

Prof. Richard Herrmann, MD

Richard Herrmann studied human medicine at the University of Heidelberg in Germany, where he completed a doctorate in 1973 and a Habilitation in internal medicine in 1985. Herrmann was head physician of the Clinic for Medical Oncology at University Hospital Basel from 1991 to 2011 as well as associate professor (Extraordinarius) in the Faculty of Medicine at the University of Basel. Today, Herrmann heads the Department of Clinical Research at University Hospital Basel. Since summer 2009 he has been the president of Oncosuisse, the Swiss Federation Against Cancer, which is responsible for development and implementation of the National Cancer Programme 2011–2015. Previously he was president of the Swiss Group for Clinical Cancer Research (SAKK) for six years (2004 to 2010). He has also been vice-president of the Cancer Research Switzerland foundation since 2009.

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Research funding by the cantonal cancer leagues

As a federation, the Cancer League comprises 19 cantonal and regional cancer leagues, with the Swiss Cancer League (SCL) as the umbrella organization with its headquarter in Bern. More than half of the cantonal cancer leagues provided funds for research in 2011, including the Bern Cancer League (BCL). The primary goals of the BCL are promotion of young researchers and targeted strengthening of Bern as a research centre.

Cancer is not only a medical but also increasingly a socio-economic problem. Cancer incidence is rising worldwide. Confronted with the challenges of cancer are the patients and their families but also primary care physicians, specialists such as surgeons, oncologists, radio-oncologists, psycho-oncologists, epidemiologists, and pathologists, basic researchers, and not least patient and health organizations and politicians. Research is needed in all areas. In this broad field, what priorities does the research committee of the BCL set for research funding, and what research projects does it fund? Like the Swiss Cancer League and the Cancer Research Switzerland foundation (CRS), the BCL focuses on supporting patient-centred research, whether in basic research, patient care (diagnosis and treatment), or prevention.

Initial funding for first-class, competitive research

Due to the limited funds available to the research committee each year (the total funds requested in the grant applications submitted exceed the funds available many times over), the committee of experts seeks mainly to promote young researchers by granting start-up funding for their research work. The grant monies are intended to give the applicants the opportunity to collect sufficient data for submitting competitive project proposals to national and international institutions such as the Swiss National Science Foundation (SNSF), the SCL and the CRS, and the European Union (EU). With this, the research commission and the board of the BCL underline their goal to conduct research funding at a high and competitive level.

The members of the research committee derive from all specialist areas in clinical and experimental cancer research. The research project applications submitted are rated by individual committee members. For each project application, the committee member in addition obtains a review from a renowned external peer expert in the particular specialist field. Once the reviews have been completed, the committee member presents the research project to the committee. Based on scientific criteria, the committee then decides whether the project is eligible for funding. We would like to take this opportunity to extend sincere thanks to all of the external experts for their voluntary, unpaid work. Without their efforts, it would not be possible for the research committee to support so many projects of outstanding quality.

Prof. George Thalmann, MD
Chairman of the research committee of the Bern Cancer League; director and chairman of the Department of Urology, University of Bern / Bern University Hospital

Strengthening Bern as a research centre

As a priority, funding is awarded to young researchers with innovative and scientifically high-quality projects. This does not mean, however, that larger projects conducted by established researchers are not funded; in fact, funding for established researchers is granted for a one- to two-year period maximum, either project-based or person-based. In 2003, for example, thanks to the generous financial support of the BCL, the tumour bank of Bern University Hospital and the University of Bern could be founded. Since then, over 13,000 samples from over 3,000 patients have been collected. With the high quality of the collection and processing of the samples as well as of the management, the Tumour Bank Bern is among the top 25% of tissues banks worldwide. The tissue samples are available to all cancer researchers in the canton of Bern and can be used in cooperation with other institutes also for larger research projects, which again makes Bern more attractive as a research centre. This is thus a small success story. In addition, the research committee can award Bern Cancer Scholarships to selected young and committed researchers and also nurses in the canton of Bern who wish to complete further education and training abroad.

Research funding by the BCL focuses on institutes and hospitals located in the canton of Bern and on young researchers in the region; in this way it complements the research funding by the SCL and CRS. This research funding at the local level allows BCL's charitable donors to identify with the cantonal organization and gives them the feeling that they are making a concrete contribution in the area of cancer. For – as also the board of the BCL is convinced – today's research is tomorrow's progress.

Prof. George Thalmann, MD

George Thalmann was named director and chairman of the Department of Urology at the University of Bern/Bern University Hospital in 2010. After graduating from the Medical School at the University of Bern, he was a resident in surgery and urology at several Swiss hospitals. Following a two-year postdoctoral research fellowship in the United States, he returned to Switzerland in 1995 and joined the Department of Urology at the University of Bern. In his work he focuses among other things on urological oncology (tumour surgery) and basic research. Thalmann has served as chairman of the research committee of the Bern Cancer League since 2010.

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List of funded research projects and institutions in 2011

The list shows the financial contributions granted in 2011.

Aargau Cancer League

Bischofberger Iren | CHF 15,000.–
Careum F+E, Departement Gesundheit, Kalaidos Fachhochschule Schweiz, Zürich
"Work & Care 2" – Reconciling employment and family care in the context of the health care system (in-depth study)

Künzler Alfred | CHF 44,500.–
Onko-Psychologie, Kantonsspital Aarau, Aarau
"Individualized psychotherapy, psycho-oncology": utilization, content and evaluation of the therapy process and the results

Wernli Martin | CHF 220,000.–
Klinische Forschung Aargau AG, Kantonsspital Aarau, Aarau
Cancer registry canton Aargau

Basel Cancer League

Bihl Michel P. | CHF 18,000.–
Departement Pathologie, Universitätsspital Basel, Basel
Analysis of ETV1 (ER81) expression in gastrointestinal stroma tumours (GISTs): its relationship with genotype and prognostic classification

Heinimann Karl | CHF 91,000.–
Forschungsgruppe Humangenetik, Universität Basel, Basel
Comprehensive genetic analysis of Lynch syndrome associated colorectal cancers by exome sequencing

Medinger Michael | CHF 7,050.–
Hämatologie, Universitätsspital Basel, Basel
Role of Dkk3 in the pathophysiology of myeloproliferative neoplasms

Mols Anke M. | CHF 8,000.–
Chirurgische Klinik, Kantonsspital Olten, Olten
Surgical procedures for advanced tumour disease: a prospective study evaluating quality of life

Niemann Tilo | CHF 50,000.–
CHRU Calmette, Department of Thoracic Imaging, Lille, France & Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
Dose reduction in computed tomography (CT). Justification and clinical evaluation of ultra low tube voltage scanning in paediatric CT and clinical evaluation of automatic tube voltage adaption

Schwaller Jürg | CHF 71,950.–
Departement Biomedizin, Universitätsspital Basel, Basel
Exploring a novel therapeutic approach for acute leukaemia by targeting LEDGF/p75

Sommer Gregor | CHF 24,000.–
Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
Development of functional imaging evaluation criteria for assessment of treatment response to the CTLA-4 antibody ipilimumab in patients with metastatic malignant melanoma and non-small cell lung cancer

Bern Cancer League

Guenat Olivier Thierry | CHF 60,000.–
Artificial Organ Center for Biomedical Engineering Research, Medizinische Fakultät, Universität Bern, Bern
Chemosensitivity testing of malignant pleural mesothelioma cancer stem cells in an in vivo like micro-environment based on a 3D cell culture microfluidic system

Klaeser Bernd | CHF 45,000.–
Universitätsklinik für Nuklearmedizin, Inselspital, Universitätsspital Bern, Bern
A new concept for breast imaging: breast-PET with multiparametric tumour characterization and visualization by integration of metabolical and morphological imaging modalities and voxel-wise kinetic modelling

Mc Kinnon Brett | CHF 65,000.–
Universitätsklinik für Frauenheilkunde, Departement für klinische Forschung, Universität Bern, Bern
Investigation of the inflammation-activated signal transduction pathways that stimulate angiogenesis in endometriosis and ovarian cancer

Ochsenbein Adrian F. | CHF 65,000.–
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
The role of CD27 and C1Rp (CD93) signalling on chronic myeloid leukaemia stem cells

Seiler Roland | CHF 49,137.–
Urologische Universitätsklinik, Inselspital, Universitätsspital Bern, Bern
Molecular profiling of treatment naïve primary urothelial bladder cancers and correlation with response to neoadjuvant chemotherapy

Shafighi Maziar | CHF 20,000.–
Forschungsgruppe Plastische Chirurgie, Departement für klinische Forschung, Inselspital, Universitätsspital Bern, Bern
LB1 – a new selective protein phosphatase 2A inhibitor to increase tissue nitric oxide concentration and to improve skin flap survival in a rat cancer model

Walter Martin A. | CHF 96,000.–
Universitätsklinik für Nuklearmedizin, Inselspital, Universitätsspital Bern, Bern
A gold-198 based nanoparticle platform for the treatment of neuroendocrine cancers

Zlobec Inti | CHF 100,000.–
Institut für Pathologie, Universität Bern, Bern
Effect of DNA methylation on Epithelial Mesenchymal Transition (EMT)-derived tumour cells (tumour budding) and the local immune response in colorectal cancer

Geneva Cancer League

Ansari Marc | CHF 140,000.–
Département de pédiatrie, Hôpitaux universitaires de Genève (HUG), Genève
Pharmacogenomics of childhood cancer

Dietrich Pierre-Yves | CHF 125,000.–
Service d'oncologie, Département de médecine interne, Hôpitaux universitaires de Genève (HUG), Genève
Identification and validation of glioma antigens: towards immunotherapies for brain tumours

Mach Nicolas | CHF 96,600.–
Service d'oncologie, Département de médecine interne, Hôpitaux universitaires de Genève (HUG), Genève
Development of a new cancer treatment concept combining two innovative approaches in the immunomodulation field: cell therapy and CTLA-4 blockage

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

Mathes Thomas | CHF 96,667.–
Service d'hématologie, Département de médecine interne, Hôpitaux universitaires de Genève (HUG), Genève
Study of the role of JAM-C in the normal differentiation of B-lymphocytes and the ontogeny of proliferative syndromes

Reith Walter | CHF 43,900.–
Département de pathologie et d'immunologie, Faculté de médecine, Université de Genève, Genève
Identification of cellular functions and genes regulated by oncogenic microRNA 155

Sappino André-Pascal | CHF 50,000.–
Service d'oncologie, Hôpitaux universitaires de Genève (HUG), Genève
The ATM gene in carcinogenesis

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

Torre 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

Walker Paul | CHF 95,527.–
Service d'oncologie, Hôpitaux universitaires de Genève (HUG), Genève
Recognition of a tumour antigen expressed by gliomas: potential of low avidity T-cell responses and immunotherapy

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: phone follow-up regarding new symptoms during treatment with oral fluoropyrimidine

Neuchâtel Cancer League

Registre neuchâtelois des tumeurs | CHF 124,887.–
Contribution to 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

Carbone Giuseppina | CHF 65,000.–
Laboratorio di oncologia sperimentale, Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
MicroRNA network regulated by ETS transcription factors in prostate cancer

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

Gamondi Claudia | CHF 15,000.–
Servizio et unità cure palliative, Istituto oncologico della Svizzera italiana (IOSI), Ospedale San Giovanni, Bellinzona
Living will: patients rights and duties of the GP

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

Vaud Cancer League

Rey-Baeriswyl Marie-Claire | CHF 19,440.–
Haute école fribourgeoise de travail social, Fribourg
A scientific and participatory approach to adjust interventions to the psychological needs of people affected by cancer

Central Switzerland Cancer League

Diebold Joachim | CHF 60,000.–
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 73,000.–
Forschungsgruppe Humangenetik, Universität Basel, Basel
Comprehensive genetic analysis of Lynch syndrome colorectal cancers by exome-wide sequencing

Allain Frédéric | CHF 53,260.–
Institut für Molekularbiologie und Biophysik, ETH Zürich, Zürich
In vitro reconstruction of Nrf2 transcription by a "Systems NMR" approach

Arni Stephan | CHF 64,512.–
Klinik für Thoraxchirurgie, UniversitätsSpital Zürich, Zürich
Activity-based protein profiling in human lung cancer biopsies

Bernasconi Michele | CHF 56,512.–
Abteilung für Infektiologie/Krebsforschung, Kinderspital Zürich, Zürich
Role of proprotein convertases in paediatric sarcomas: useful theragnostic targets?

Bornhauser Beat | CHF 57,196.–
Forschungsgruppe Leukämie/Onkologie, Kinderspital Zürich, Zürich
Large scale drug response profiling to identify new targets in refractory leukaemia

Favrot Claude | CHF 86,602.–
Klinik für Kleintiermedizin, Universität Zürich, Zürich
Characterization of newly discovered canine papillomavirus 3 (CPV3) and assessment of its carcinogenic potential

Felley-Bosco Emanuela | CHF 51,353.–
Labor für molekulare Onkologie, UniversitätsSpital Zürich, Zürich
Sonic hedgehog signalling in malignant pleural mesothelioma

Gorr Thomas | CHF 70,352.–
Institut für Veterinärphysiologie, Universität Zürich, Zürich
Chorio-allantoic membrane assay for preclinical cancer therapy screening: simultaneous targeting of tumour vasculature and the metabolic symbiosis between oxygenated and hypoxic tumour cells

Grotzer Michael | CHF 117,317.–
Abteilung Neuroonkologie, Kinderspital Zürich, Zürich
Tumourigenic potential of the MYC target gene JAG2 in childhood medulloblastoma

Lopes Massimo | CHF 58,755.–
Institut für molekulare Krebsforschung, Universität Zürich, Zürich
Structural and genomic insights into oncogene-induced DNA replication stress

Müller Anne | CHF 64,036.–
Institut für molekulare Krebsforschung, Universität Zürich, Zürich
Prevention of gastric cancer through the development of a Helicobacter pylori-specific vaccine

Samaras Panagiotis | CHF 13,000.–
Klinik für Onkologie, UniversitätsSpital Zürich, Zürich
Mobilization of CD34⁺ cells with a standard dose of Filgrastim after Vinorelbine in patients with multiple myeloma. A prospective randomized unicentric phase II study

Weller Michael | CHF 35,500.–
Klinik für Neurologie, UniversitätsSpital Zürich, Zürich
A population-based study on the incidence, prognosis and molecular genetics of patients with glioblastoma in the canton of Zurich

Aargau Cancer League

Bischofberger Iren | **"Work & Care 2" – reconciling employment and family care in the context of the health care system (in-depth study)**
Careum F+E, Departement Gesundheit, Kalaidos Fachhochschule Schweiz, Zürich
Duration: 01.05.2010 – 01.07.2012

Reconciling employment and family care is not only influenced by employers' and employees' perspectives, which was the research focus of the "Work & Care 1" study (2007–2009). Equally important is the influence of the health care system on reconciling. This in-depth study therefore focuses on various illness trajectories and different health care settings. Three research partners in the Aargau region were invited to participate: Rehab Clinic Barmelweid, specialized Geriatric and Nursing Care Lindenfeld, and Aargau Cancer League and its specialized oncology home care service. Qualitative and quantitative research methods were used with the three partners and produced findings for reconciling employment and care in the settings of acute inpatient care, long-term care, and in-home care. The data focused on working family caregivers in the context of heart diseases, geriatric conditions, and cancer. Also, follow-up interviews with family caregivers from the first research study provided longitudinal data on reconciling arrangements in the context of dementia.

Künzler Alfred | **"Individualized psychotherapy, psycho-oncology": utilization, content and evaluation of the therapy process and the results**
Onko-Psychologie, Kantonsspital Aarau, Aarau
Duration: 01.10.2010 – 31.12.2011

One-third of patients with cancer experience great psychological burden and often do so for a long period of time. The same is true for their spouses/partners. The project framework on which this study builds examined the psychological impact of cancer on the patients and on their partners. The main result showed that the female partners of male cancer patients are the most affected and are often more strongly affected than female cancer patients. One part of the male patients and their partners (about 50%) participates in oncological psychotherapy. This monitoring does not follow any pattern but is based on individual problems. As there has been very little research on this form of psychotherapy, we do not know how helpful it can be. This study examines individual oncological psychotherapy with regard to utilization (who goes to psycho-oncology), content (what is talked about), process (what happens in psycho-oncology therapy), and effects (what is the result).

Wernli Martin | **Cancer Registry Canton Aargau**
Klinische Forschung Aargau AG, Kantonsspital Aarau, Aarau

On December 14, 2010, the Great Council of the Canton Aargau approved an operation loan of CHF 685,000 per year for the creation of a Cantonal Cancer Registry. The construction of the registry was supported by all political parties and approved by 109 votes to 13. The agreement came after two-years of preparation and explanation work by the cantonal cancer league Aargau. The entire structure of the registry, from the conceptual work to the future proper infrastructure, was funded by the Aargau Cancer League. The data collection started in summer 2012. The Cancer Registry Aargau is a very important step towards the construction of a national registry.

Basel Cancer League

Bihl Michel P. | **Analysis of ETV1 (ER81) expression in gastrointestinal stromal tumours (GISTs): its relationship with genotype and prognostic classification**
Departement Pathologie, Universitätsspital Basel, Basel
Duration: 01.07.2011 – 30.06.2012

We are now in the era of "personalized medicine", and gastrointestinal stromal tumours (GISTs) are a perfect example of this new approach in therapy. The therapeutic response correlates strictly with well-known genetic alterations in CKIT and PDGFRA genes. Highly specific drugs target tumour cells selectively and therefore improve the prognosis of a given patient considerably. However, tumour relapses arise in 50% of the cases after two years. Factors other than CKIT and PDGFRA mutations may contribute to this phenomenon. ETV1, a newly described marker in GIST, is involved in the pathogenesis and prognosis of several tumours and is therefore a candidate of choice. Our project aims to verify ETV1 expression in early and advanced GIST and additionally to assess the relationship of ETV1 expression to other genetic alterations. This will aid understanding of acquired resistance to therapy in GIST and may point to new drug targets.

Heinimann Karl | **Comprehensive genetic analysis of Lynch syndrome-associated colorectal cancers by exome sequencing**
Forschungsgruppe Humangenetik, Universität Basel, Basel
Duration: 01. 10. 2011–31. 09. 2012

Based on a set of more than 190 tumour samples from verified Lynch syndrome (also referred to as HNPCC) carriers, we are screening the coding gene sequences of colorectal cancers for the presence of pathogenic mutations using novel massively parallel sequencing technologies. Our aim is to identify "key genes" and affected signalling pathways – and to compare these with carcinogenesis in sporadic (not hereditary) colorectal cancers. We hope that the genetic identification and biological characterization of the signalling pathways will provide a better understanding of hereditary and sporadic tumourigenesis – and lead to novel ideas for therapeutic and preventive measures in the treatment of colorectal cancer.

Medinger Michael | **Role of Dkk3 in the pathophysiology of myeloproliferative neoplasms**
Hämatologie, Universitätsspital Basel, Basel
Duration: 01. 05. 2011–01. 08. 2012

Dickkopf-3 (Dkk3) has been proposed as a tumour suppressor gene and a marker for tumour blood vessels. We found Dkk3 expression in platelets and megakaryocytes from healthy controls and patients with *BCR-ABL1*-negative myeloproliferative neoplasms (MPN). Significantly more $Dkk3^+$ megakaryocytes could be found in bone marrow biopsies from patients with MPN (essential thrombocythemia, polycythemia vera (PV), primary myelofibrosis (PMF)) than in controls. $Dkk3^+$ megakaryocytes correlated with microvessel density in PV and PMF. We conclude that Dkk3 might be involved in the pathogenesis of MPN. In our proposal we will analyse the function of Dkk3 in platelets from MPN patients. As the clinical course of MPNs, and particularly of PV and ET, is characterized by a thrombophilic state that manifests with microcirculatory disturbances and arterial and venous thromboses, the influence of Dkk3 on platelet aggregation and haemostasis will be investigated.

Mols Anke M. | **Surgical procedures for advanced tumour disease: a prospective study evaluating quality of life**
Chirurgische Klinik, Kantonsspital Olten, Olten
Duration: 01. 04. 2011–31. 03. 2013

We are evaluating the impact of palliative surgical procedures on quality of life (QoL) in tumour-related palliative settings. Here local tumour growth may produce severe symptoms. In clinical practice we need to answer the question as to whether operative interventions or conservative management preserve more quality of life. We are evaluating QoL before and after operative interventions and recording the clinical course.

Niemann Tilo | **Dose reduction in computed tomography (CT): justification and clinical evaluation of ultra-low tube voltage scanning in paediatric CT and clinical evaluation of automatic tube voltage adaption**
CHRU Calmette, Department of Thoracic Imaging, Lille, France & Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
Duration: 01. 09. 2011–31. 08. 2012

The increasing use of CT scanners raises concerns about the increasing radiation dose applied to the population. As its use has risen substantially, CT is today the main contributor of medical radiation to the general population. The main objective of this project is to evaluate new dose reduction techniques in chest CT based on lower kV exposure. Since children are more sensitive to radiation than adults, a part of our project aims to justify and evaluate low tube voltage scanning with 70 kV (instead of 80 kV) that will allow substantial paediatric dose reduction in future. Another part of this study aims at dose reduction also in adults by automated tube voltage adaption that will decrease radiation in combination with tube current modulation. Because dose reduction implies deterioration of image quality, we focus on optimization of quality parameters in combination with diagnostic radiation dose reduction (as low as is reasonably achievable).

Schwaller Jürg | **Exploring a novel therapeutic approach for acute leukaemia by targeting LEDGF/p75**
Departement Biomedizin, Universitätsspital Basel, Basel

Mixed lineage leukaemia (MLL) fusions are a molecular hallmark of infant acute leukaemia with poor prognosis. MLL-fusions induce leukaemia through aberrant genetic programs mediated by a large protein complex tethered to chromatin by the lens epithelial-derived growth factor (LEDGF/p75). LEDGF/p75 is known as a nuclear factor for human immunodeficiency virus 1 (HIV1) replication by tethering the viral integrase to chromatin. As expression of the integrase-binding domain (IBD) of LEDGF/p75 impairs viral replication, we asked whether expression of the LEDGF/p75 IBD might impair growth of leukaemic cells. We identified two small stretches in the LEDGF/p75 IBD that when overexpressed disrupted the interaction between the MLL fusion and LEDGF/p75 and significantly impaired growth of leukaemic cells in cultures and in a mouse model. These observations provide a rationale to screen for small molecules targeting MLL acute leukaemia.

Sommer Gregor | **Development of functional imaging evaluation criteria for assessment of treatment response to the CTLA-4 antibody ipilimumab in patients with metastatic malignant melanoma and non-small cell lung cancer**
Klinik für Radiologie und Nuklearmedizin, Universitätsspital Basel, Basel
Duration: 01.06.2011–31.03.2013

Tumour response to chemotherapy is commonly assessed with radiologic imaging using computed tomography (CT), where the sizes of predefined lesions are measured according to international standards (WHO/RECIST). This is important, as it allows for an early decision on success or failure of a treatment. However, follow-up of tumour size alone is not sufficient for assessing the effects of modern cancer therapies such as antibodies targeted to the immune system (T-cells). The aim of this study is therefore to develop new criteria for treatment response that are tailored to the specific properties of targeted immunotherapies and also include tissue properties like cellular density. The method that is used for this purpose is diffusion weighted magnetic resonance imaging, which has higher soft tissue contrast and thus allows for better tissue characterization than CT.

Bern Cancer League

Guenat Olivier Thierry | **Chemosensitivity testing of malignant pleural mesothelioma cancer stem cells in an *in vivo*-like microenvironment based on a 3D cell culture microfluidic system**
Artificial Organ Center for Biomedical Engineering Research, Medizinische Fakultät, Universität Bern, Bern
Duration: 01.02.2012–01.08.2013

Malignant pleural mesothelioma (MPM) is a lethal cancer of the protective lining that covers many internal organs of the body. It has high chemotherapeutic resistance via unknown mechanisms. A prevailing hypothesis is that cancer stem cells (CSCs) persist in tumours, causing relapse after chemotherapy. Here, we propose a novel *in vitro* method to study CSCs, enabling a better reproduction of the three-dimensional nature of tumours. This method will combine microfluidics to allow the accurate delivery of drugs and spheroids to approximate the cell-cell interactions. Ultimately, the evaluation of drug response to multiple agents will define the best sequential or simultaneous administration of available agents to be to eradicate CSCs the most effectively. It is expected that this approach will improve the outcomes of MPM treatments and could also be applied to other solid tumours.

Klaeser Bernd | **A new concept for breast imaging: breast PET with multiparametric tumour characterization and visualization by integration of metabolic and morphological imaging modalities and voxel-wise kinetic modelling**
Universitätsklinik für Nuklearmedizin, Inselspital, Universitätsspital Bern, Bern
Duration: 01.10.2010–01.04.2013

Currently available breast imaging, including MRI, offers only moderate specificity. False-positive MRI detection was shown to lead to extended treatment in 30% of patients. We plan to develop software capable of providing visualizations of multiparametric image data, meaning time-resolved imaging with high spatial resolution of different metabolites. This software will be tested with 40 patients, and it is hoped that it will reduce the risk of overtreatment.

Mc Kinnon Brett | **Investigation of the inflammation-activated signal transduction pathways that stimulate angiogenesis in endometriosis and ovarian cancer**
Universitätsklinik für Frauenheilkunde, Departement für klinische Forschung, Universität Bern, Bern
Duration: 01.01.2012–01.01.2014

Ovarian cancer is the fifth most common cause of all cancer deaths. This is in part due to the fact that 75% of ovarian cancers are detected at advanced stages. Endometriosis, the growth of ectopic endometrial tissue, is a benign but painful condition that affects 10–20% of women. It has been associated with ovarian cancer. This could be because inflammation is linked to malignancy, as it can stimulate carcinogenic processes, such as angiogenesis: the formation of new blood vessels. We propose to study the relationship between inflammation and malignancy development through angiogenesis, using endometriosis as a model of an inflammatory premalignant state.

Ochsenbein Adrian F. | **The role of CD27 and C1Rp (CD93) signalling on chronic myeloid leukaemia stem cells**
Universitätsklinik für Medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
Duration: 01.08.2011–01.08.2013

Chronic myeloid leukaemia (CML) is a disorder caused by the transformation of a leukaemia stem cell (LSC). This disease is associated with the Philadelphia chromosome, a reciprocal translocation between chromosomes 9 and 22 that produces an aberrant protein BCR/ABL. The only curative treatment for CML is bone marrow transplantation. For unknown reasons, CML is one of the most sensitive leukaemias to the beneficial effect of the transplantation, using the immune system to destroy the cancer. We propose to investigate how LSCs provoke an immune response. Our study will lead to potential therapeutic targets.

Seiler Roland | **Molecular profiling of treatment-naïve primary urothelial bladder cancers and correlation with response to neoadjuvant chemotherapy**
Urologische Universitätsklinik, Inselspital, Universitätsspital Bern, Bern
Duration: 01. 01. 2012–01. 01. 2013

At diagnosis, about 30 % of patients with urothelial bladder cancer present with invasive disease, and 15 % are metastatic. For those patients, neoadjuvant chemotherapy improves 5-year overall survival. Only patients with complete response after chemotherapy, which is rare, have a good outcome. Improvement in outcome might be achieved if patients' likelihood of response could be determined. We plan to correlate different biological phenotypes of cells before treatment with response rates by molecular profiling. This project will translate molecular tumour profiles into clinically relevant information on the chemosensitivity of bladder cancers. This might aid identification of cancers that respond to neoadjuvant chemotherapy as well as cancers that are chemoresistent and should undergo immediate surgery. In addition, this might specify the role of targeted therapies in the neoadjuvant setting.

Shafighi Maziar | **LB1 – a new selective protein phosphatase 2A inhibitor to increase tissue nitric oxide concentration and to improve skin flap survival in a rat cancer model**
Forschungsgruppe Plastische Chirurgie, Departement für klinische Forschung, Inselspital, Universitätsspital Bern, Bern
Duration: 01. 07. 2011–01. 01. 2013

Delayed wound healing after tumour surgery precludes patients from chemotherapy or radiotherapy, which in turn might have an impact on survival. Reconstructive surgery research has focused on improving angiogenesis, the formation of new blood vessels. However, since angiogenesis also supports tumour growth, angiogenic factors are not used in oncology patients. A new inhibitor named LB1 has been developed recently. LB1 has been shown to decrease tumour growth and lower recurrence rate in combination with chemotherapeutical agents. In addition, it increases wound healing in rats. We plan to expand this research to study the effect of LB1 in an oncological model. The goal of this study is the oncologically safe use of LB1 to improve results in surgery and therefore to decrease delay of treatment.

Walter Martin A. | **A gold-198 based nanoparticle platform for the treatment of neuroendocrine cancers**
Universitätsklinik für Nuklearmedizin, Inselspital, Universitätsspital Bern, Bern
Duration: 01. 01. 2012–01. 01. 2015

Neuroendocrine tumours arise from cells of the hormonal and nervous system. They are treated with radiopeptide therapy, a special form of radiotherapy. To increase the number of emitting atoms into the tumour cell, we propose to use gold-198. We hypothesize that gold-198 nanoparticles allow targeting and treatment of cancer cells *in vitro* and *in vivo* and offer a distribution into the body superior to that of the clinically used radiopeptides, improving the overall efficacy and toxicity profile of radiopeptide therapy. Successful completion of this project will significantly increase treatment efficacy by targeted tumour delivery of higher therapeutic doses. Further, once established, this platform would offer additional potential applications.

Zlobec Inti | **Effect of DNA methylation on epithelial-mesenchymal transition (EMT)-derived tumour cells (tumour budding) and the local immune response in colorectal cancer**
Institut für Pathologie, Universität Bern, Bern
Duration: 01. 09. 2011–01. 03. 2013

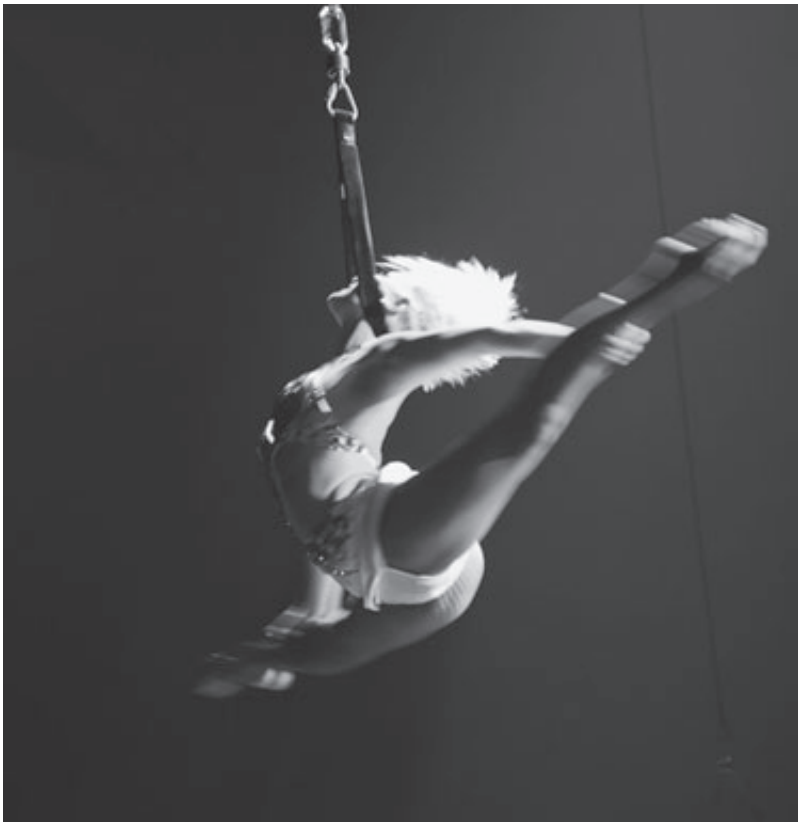
Tumour budding is recognized as an adverse prognostic factor, as it is linked with metastasis. What triggers tumour budding in colorectal cancer is not known. Epigenetic modification is a hereditable modification that does not alter the DNA sequence but changes gene expression or cellular phenotype. Epigenetic modifications, such as methylation, are emerging as key regulators of colorectal tumourigenesis. It has been shown recently that the negative effect of tumour budding can be countered by the presence of specific immune responses at the budding site. We plan to study the relationship between high-level epigenetic modifications, the presence of tumour budding and the local immune response.

Geneva Cancer League

Ansari Marc | **Pharmacogenomics of childhood cancer**
Département de pédiatrie, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01. 01. 2011–31. 12. 2011

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. 2011

Mach Nicolas | **Development of a new cancer treatment concept combining two innovative approaches in the immunomodulation field: cell therapy and CTLA-4 blockage**
Service d'oncologie, Département de médecine interne, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01. 01. 2010–31. 12. 2011



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

Mathes Thomas | **Study of the role of JAM-C in the normal differentiation of B-lymphocytes and the ontogeny of proliferative syndromes**
Service d'hématologie, Département de médecine interne, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01. 01. 2009–31. 12. 2011

Reith Walter | **Identification of cellular functions and genes regulated by oncogenic microRNA 155**
Département de pathologie et d'immunologie, Faculté de médecine, Université de Genève, Genève
Duration: 01. 01. 2009–01. 12. 2011

Sappino André-Pascal | **The ATM gene in carcinogenesis**
Service d'oncologie, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01. 01. 2011–31. 12. 2011

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

Torre 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

Walker Paul | **Recognition of a tumour antigen expressed by gliomas: potential of low avidity T-cell responses and immunotherapy**
Service d'oncologie, Hôpitaux universitaires de Genève (HUG), Genève
Duration: 01. 01. 2009–31. 12. 2011

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

Grisons Cancer League

von Moos Roger | **Patient management study: phone follow-up regarding new symptoms during treatment with oral fluoropyrimidine**
Medizinische Onkologie und Hämatologie, Kantonsspital Graubünden, Chur
Duration: 01. 09. 2011–31. 12. 2012

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 learn how to deal with side effects and know what they can do about them. As a result, discontinuations and treatment interruptions are 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 tumour registry in Neuchâtel 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/year) and by the Neuchâtel Cancer League.

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: 2011–2012

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

Carbone Giuseppina | **MicroRNA network regulated by ETS transcription factors in prostate cancer**
Laboratorio di oncologia sperimentale, Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Duration: 2011

This project analysed transcription of specific genes implicated in prostate cancer.

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: 2011–2013

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, aiming at identifying patients that could benefit from those treatments.

Gamondi Claudia | **Living will: patients' rights and GPs' duties**
Servizio et unità cure palliative, Istituto oncologico della Svizzera italiana (IOSI), Ospedale San Giovanni, Bellinzona
Duration: 2010–2011

Patients should complete a living will in the form of written instructions stating their intentions regarding medical treatment in case they are no longer able to express them later. Although in 2013 a federal law will make living wills mandatory, few patients have completed living will up to now. Ticino has decided to participate in a multicentre study conducted by Dr. Sophie Pautex at the University Hospital Geneva. The objective of this study is to elucidate the factors influencing the patient's decision to prepare a living will. In Ticino, the study aims to interview some patients in palliative care units in hospitals, hospices or in-home care. A social worker (supported at 20 % by the Ticino Cancer League) will talk with patients and relatives about their wishes regarding their involvement in medical decisions and living wills.

Grassi Fabio | **Purinergic signalling in the pathophysiology of central nervous system infiltration in T-cell leukaemia**
Istituto di ricerca in biomedicina (IRB), Bellinzona
Duration: 2011–2013

The project aims at analysing 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 in this leukaemia, typically occurring 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: 2011–2013

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.

Vaud Cancer League

Rey-Baeriswyl Marie-Claire | **A scientific and participatory approach to adjusting interventions to the psychological needs of people affected by cancer**
Haute école fribourgeoise de travail social, Fribourg
Duration: 01.01.2008–01.03.2012

The League commissioned a study to rethink its social service activities, especially their location within hospitals, and the development of psychosocial oncology services. An evaluation of professional practices identified the logic of the contributions currently in place. A study on needs tried to understand the reality of persons affected; taking a qualitative, comprehensive sociological approach, it cross-referenced their standpoint (patients, relatives, bereaved) and those of the stakeholders (medical professionals, volunteers, social workers).

The study highlighted the effects of the disease for all actors and their ways of coping; it identified the challenges encountered, the resources mobilized, and what was perceived as inadequate or missing support in six "domains" (experience of illness – social network – work – health care system – family – finances). These were then translated into intervention expectations, pointing out the necessity to act at several levels, including the individual situation as well as the context leading to the difficult situation.

- Expectations (information, mediation) regarding interventions for individuals and their environments underline the necessity to prioritize situations of social vulnerability.
- Most expectations are about interventions on services production mechanisms and institutional contexts (anticipating needs, organization and adaptation of resources), aiming at diminishing whatever generates disability or discrimination situations and fostering participation and social integration.
- Expectations regarding structural interventions (planning, evaluation) concern the maintenance of solidarity and community life (working on the disease representation, recognition of rights, social protection).

Support for organizational development favours adjusting interventions to fit the stated needs.

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: 01.11.2011–01.11.2014

Based on the numbers of the central Swiss cancer registry, 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: 01.03.2011–01.03.2013

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.

Zurich Cancer League

Allain Frédéric | ***In vitro* reconstruction of Nrf2 transcription by a "Systems NMR" approach**
Institut für Molekularbiologie und Biophysik, ETH Zürich, Zürich
Duration: 01.11.2011–30.10.2012

The formation of cancer requires simultaneous change in the expression of several proteins that allow cancer cells to proliferate continuously and to escape the cell cycle control as well as to cover their increased metabolic requirements. The goal of this project is the development of a new method for the *in vitro* reconstruction of the protein networks, using NMR spectroscopy. This will lead to a better understanding of the physiological and pathological states of these networks. In addition, this could contribute to new strategies of cancer treatment based on the reconstruction generated by the models, and their effects will be investigated at the level of the entire protein network and not only of the network's individual components.

Arni Stephan | **Activity-based protein profiling in human lung cancer biopsies**
Klinik für Thoraxchirurgie, UniversitätsSpital Zürich, Zürich
Duration: 01. 05. 2011–30. 04. 2012

Lung cancer is the most common cause of cancer deaths worldwide. The stage of the disease is defined according to the TNM Classification of Malignant Tumours (tumour, lymph nodes, and metastasis), but nevertheless, the result varies strongly. The goal of this study is the discovery of relevant biological markers that can optimize the TNM classification system. We were able to implement a platform for the identification of clinical biomarkers based on the serine hydrolase activity. The aim of this project is to validate this finding with a larger sample size, with selective reaction monitoring (SRM) to increase the statistical reliability of the model.

Bernasconi Michele | **Role of proprotein convertases in paediatric sarcomas: useful theragnostic targets?**
Abteilung für Infektiologie/Krebsforschung, Kinderspital Zürich, Zürich
Duration: 01. 06. 2011–31. 05. 2012

There are special requirements in treatment of tumour disease in children, because the excessive use of chemotherapy, and most of all radiotherapy, can lead to serious late side effects. The goal of our research is to identify new therapeutic options. We have identified a family of proteases (proteolytic enzymes) that play an important role in the growth of paediatric sarcomas. We will study more closely the function of these proteases in paediatric sarcomas to be able to decide whether, and if so which, could be critical for a new therapy.

Bornhauser Beat | **Large-scale drug response profiling to identify new targets in refractory leukaemia**
Forschungsgruppe Leukämie/Onkologie, Kinderspital Zürich, Zürich
Duration: 01. 01. 2012–31. 12. 2012

With a new automated microscopy platform, we investigate the response profile of cancer cells of a target group of patients with highly resistant or treatment-refractory leukaemias to hundreds of different new drugs. The aim is to develop new treatment strategies.

Favrot Claude | **Characterization of newly discovered canine papillomavirus 3 (CPV3) and assessment of its carcinogenic potential**
Klinik für Kleintiermedizin, Universität Zürich, Zürich
Duration: 01. 01. 2011–31. 12. 2011

CPV3 is a papillomavirus that was recently found in a dog with epidermodysplasia verrucifomis-like changes. The goal of this study is to shed light on the carcinogenic potential of CPV3 and the mechanisms involved. To this end, the viral genes will be expressed under different conditions in dog keratinocytes (skin cells), and the effects will be studied.

Felley-Bosco Emanuela | **Sonic hedgehog signalling in malignant pleural mesothelioma**
Labor für molekulare Onkologie, UniversitätsSpital Zürich, Zürich
Duration: 01. 09. 2011–31. 08. 2012

40 % of mesotheliomas carry NF2 gene mutations, which lead to inactivation of the merlin gene. Animal models experiments showed that a perturbation of the NF2 signalling pathway together with the absence of Ink4a is essential for the development of mesotheliomas. Merlin activates the Hippo signalling pathway, which is necessary to avoid unfavourable growth, stimulated by the sonic hedgehog stem cell signalling pathway. The goal is to characterize the effect of the sonic hedgehog inhibitors on cell proliferation.

Gorr Thomas | **Chorioallantoic membrane assay for preclinical cancer therapy screening: simultaneous targeting of tumour vasculature and the metabolic symbiosis between oxygenated and hypoxic tumour cells**
Institut für Veterinärphysiologie, Universität Zürich, Zürich
Duration: 01. 10. 2011–30. 09. 2012

AH-activated molecular processes, which are responsible for the growth inhibition of the primary tumour or the propagation of malignant cells, are poorly understood. For this study, we use the chorioallantoic membrane (CAM) of live chick embryo as tumour host tissue. In the initial phase we were able to show that CAM model reflects well central clinical features of neoplasms: explanted tumours with local oxygen deficiency (hypoxia) and active angiogenesis. We were able to demonstrate that explanted breast carcinoma or melanoma that were treated with the AH antibody bevacizumab actually showed a decreased blood flow rate compared to control tumours. We want to understand whether such interventions actually reduce the tissue oxygen levels and thereby contribute to the selection of hypoxia-tolerant clones. Pharmacologically effective therapy against hypoxic tumours should then be tested. With the resulting knowledge, physicians should be able to recommend more effective anti-cancer approaches that are also associated with lower risk.

Grotzer Michael | **Tumourigenic potential of the MYC target gene JAG2 in childhood medulloblastoma**
Abteilung Neuroonkologie, Kinderspital Zürich, Zürich
Duration: 01. 01. 2012–31. 12. 2012

We explore the mechanisms of action of JAG2 and the thereby activated NOTCH signalling pathway in medulloblastoma, the most common paediatric malignant brain tumour. We study whether this signalling pathway is related to the aggressive progress of the medulloblastoma.

Lopes Massimo | **Structural and genomic insights into oncogene-induced DNA replication stress**
Institut für molekulare Krebsforschung, Universität Zürich, Zürich
Duration: 01. 07. 2011–30. 06. 2012

Pathological changes in the genetic information are the characteristic features of each tumour cell. These changes and associated DNA damages are detectable at an early stage after activation of certain oncogenes and thus occur in the earliest stages of tumourigenesis. However, the parts of the genetic information that are particularly susceptible to those damages as well as the lesions that underlie those changes are only broadly described. To fill this gap in our understanding of carcinogenesis, we identified a high-throughput method (ChiP-Seq) using established markers of DNA damage of all sections of DNA that show such damage after oncogene activation. The bioinformatics analysis of the data will allow us to determine the characteristic features of these sequences and thus make a significant contribution to our understanding of the early process of tumourigenesis.

Müller Anne | **Prevention of gastric cancer through the development of a *Helicobacter pylori*-specific vaccine**
Institut für molekulare Krebsforschung, Universität Zürich, Zürich
Duration: 01. 01. 2012–31. 12. 2012

Chronic colonization of the stomach with the human pathogen *Helicobacter pylori* represents a major risk factor for the development of gastric cancer. The goal of our research is therefore to elucidate the protective mechanisms of a *Helicobacter*-specific experimental vaccination and to identify the *Helicobacter*-antigen appropriate for use of the vaccination in humans.

Samaras Panagiotis | **Mobilization of CD34⁺ cells with a standard dose of filgrastim after vinorelbine in patients with multiple myeloma: a prospective randomized unicentric phase II study**
Klinik für Onkologie, UniversitätsSpital Zürich, Zürich
Duration: 01. 07. 2011 – 30. 06. 2012

Is less more? This project is studying the optimal dose of growth factors for the mobilization of stem cells from planned high-dose chemotherapy in patients with multiple myeloma.

Weller Michael | **A population-based study on the incidence, prognosis and molecular genetics of patients with glioblastoma in the canton of Zurich**
Klinik für Neurologie, UniversitätsSpital Zürich, Zürich
Duration: 01. 01. 2012–31. 12. 2012

This project aims to prove that the quality of life and survival of all patients in the canton of Zurich has improved due to the new development in the treatment of malignant brain tumour, glioblastomas. The project is based on the collection of data on the disease process and the collection of tumour tissue to verify the diagnosis as well as to compare the molecular changes in the tumour in the disease process. It will cover patients from the canton of Zurich that were diagnosed with a glioblastoma between 2005 and 2009.

Programme research: Supporting translational and clinical research

Since 2003 the Cancer Research Switzerland foundation (formerly Oncosuisse) has supported translational and clinical research with two funding programmes: Collaborative Cancer Research Projects (CCRP) and International Clinical Cancer Research Groups (ICP). The aim of both the CCRP and ICP is to support collaboration among different research disciplines and institutes at the national level – and in the case of the ICP at the international level.

Collaborative Cancer Research Projects (CCRP)
The CCRP are multidisciplinary research collaborations with a longer-term duration of five or more years. The focus is on supporting translational research studies that shorten the way from the laboratory to the hospital bed and thus seek to boost medical progress. The research projects are often complex and made up of several subprojects that are conducted at different institutes. The aim is 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.

International Clinical Cancer Research Groups (ICP)
The ICP are international clinical research groups in which researchers and physicians in several countries work together. These international research projects have their centres in Switzerland, where they are coordinated and managed. A research group in the ICP programme receives funding of maximum CHF 200,000 per year, or a total of CHF 800,000 over the four years of the project duration.

Since the launching of the CCRP and ICP, total grants of CHF 14.7 million have been provided for programme research (in the period 2004 to 2010), of which CHF 10.1 million went to six CCRP and CHF 4.6 million went to seven ICP. The CCRP, which earmarked large funds, were discontinued in 2009 in favour of the better manageable funding of individual projects. ICP calls for proposals are also no longer being announced. Instead, since 2009 funding has been given to clinical research institutions via research contracts and agreements (see here the article on research funding on page 6).

Kurt Bodenmüller
Communications manager of the Scientific Office, Swiss Cancer League

Collaborative Cancer Research Projects (CCRP)

List of completed or ongoing research projects

Hemmings Brian A. | CCRP OCS 01613-12-2004 | CHF 2,076,200.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Development of molecular strategies for therapeutic interference with glioblastomas

Rüegg Curzio et al. | CCRP OCS 01812-12-2005 | CHF 2,209,500.–
Division de pathologie expérimentale, Université de Fribourg, Fribourg
Tumour-mediated mobilization of bone marrow cells: implications in tumour angiogenesis, lymphangiogenesis and metastasis, and disease monitoring

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 or ongoing research projects in brief

Hemmings Brian A. | **Development of molecular strategies for therapeutic interference with glioblastomas**

KFP OCS 01613-12-2004
Duration: 01.01.2006–01.09.2011
CHF 2,076,200.–

Glioblastoma multiforme (GBM) is the most aggressive and lethal form of brain cancer, with a mean patient survival time of approximately one year. Therefore, there is currently an urgent need to identify the molecular mechanisms of therapy resistance and driving pathways that might be the Achilles heel of GBM.

In a search for novel molecular targets, our kinome-focused microarray analysis identified overexpressed protein kinase in fresh brain tumours including primary and secondary glioblastoma, astrocytoma and oligodendroglioma. The study identified targets highly overexpressed in tumour samples, cancer spheres and cell lines that have been previously associated with gliomagenesis (e.g. EGFR or PDGFR), as well as novel kinases such as MAP kinase-interacting kinase 1 (MNK1), Mer receptor tyrosine kinase (MerTK) and spleen tyrosine kinase (SYK), which have not been previously reported in GBM.

MNK1 is involved in the regulation of protein synthesis. It phosphorylates the translation initiation factor eIF4E on Ser 209 that is required for the eIF4E oncogenic activity in cancers. Targeting MNK1 together with mTORC1 inhibitor rapamycin or RAD001 induced cell cycle arrest and strongly inhibited global translation and GBM cell proliferation. Our recent study validated a therapeutic approach based on concomitant targeting of MNK1 and mTORC1 pathways in the orthotopic GBM mouse model. Furthermore, microarray analysis of total and polysomal RNA from MNK1-depleted GBM cells identified mRNAs involved in regulation of the TGF-β pathway. Translation of SMAD2 as well as TGF-β-induced cell motility was regulated by MNK1 signalling. Our findings offer insights into how MNK1 pathways converge with TGF-β pathways and regulate glioma cell motility. Furthermore, they suggest including MNK1-controlled translational pathway inhibition in targeted therapies to treat GBM more effectively.

MerTK and SYK, which are normally exclusively expressed in haematopoietic cells, were found on GBM tumour cells. Activated MerTK increased glioma cell infiltrative potential through regulating actomyosin contractility. In addition, DNA damage robustly triggered the upregulation and phosphorylation of MerTK, which protected cells from apoptosis. This effect was strongly impaired upon MerTK depletion or overexpression of an inactive MerTK mutant. SYK was found strongly activated at the membrane after EGF treatment and treatment with three specific small molecule inhibitors, and siRNA targeting SYK

strongly blocked proliferation and migration of GBM cells. This was confirmed through wtSYK and kinase-dead SYK overexpression. In addition, SYK was found to regulate cell cycle progression, and SYK overexpressing cells were more resistant to etoposide treatment. MerTK and SYK were found to be absent in normal brain tissues, indicating that inhibition may have maximal effects on the disease state with minimal toxicity. We will therefore further investigate their role in GBM through the use of orthotopic and syngeneic animal models to establish optimal therapeutic interference.

Our study analysed signalling networks and has been the platform to establish the potential of identified deregulated pathways for development of novel targeted therapies, as well as diagnostic and prognostic markers for gliomas with the ultimate goal to improve the quality of life of brain cancer patients.

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Rüegg Curzio et al. | **Tumour-mediated mobilization of bone marrow cells: implications in tumour angiogenesis, lymphangiogenesis and metastasis, and disease monitoring**

KFP OCS 01812-12-2005
Duration: 01.11.2006–01.11.2011
CHF 2,209,500.–

Whereas today localized cancer can be cured with a good success rate, metastatic, advanced cancers remain difficult to cure. The ability to detect and interfere with invasion and metastasis may open up new diagnostic, prognostic and therapeutic opportunities. The formation of "tumour vasculature" (i.e., tumour angiogenesis) is an important event contributing to tumour growth and metastasis. Bone marrow-derived progenitor and inflammatory cells are attracted to tumour sites to promote tumour angiogenesis, invasion and metastasis though the release of growth factors, but the mechanisms involved are not fully understood. Many important questions regarding the use of anti-angiogenic drugs in patients remain open, in particular how to monitor their efficacy and how to detect the development of resistance.

Goal
The overarching goal of the project is to identify mechanisms by which bone marrow-derived cells promote tumour progression and metastasis as a basis for the development of novel therapeutic approaches to suppress metastasis. A secondary goal is to use these cells as indicators of tumour angiogenesis and metastatic spreading for early diagnosis and monitoring of cancer progression and therapy.

Methods
To address these questions we will combine *in vitro* molecular and cellular experiments, animal models and clinical studies. In animal models we will study the effect of the growing tumour on the mobilization of bone marrow-derived cells and of therapeutic interventions. In cell culture experiments we will investigate changes in the function of these cells, and we will modify them to validate mechanisms. Further, we will analyse bone marrow-derived cells in the peripheral blood of patients before and after treatments to validate *in vitro* the experimental results. Animal experiments are limited to the bare minimum and whenever possible replaced with experiments in culture and analyses of human samples.

Results
We identified different bone marrow-derived cell subpopulations that are capable of promoting angiogenesis, lymphangiogenesis and metastasis. These cells may serve as candidate biomarkers for these events but also as potential therapeutic targets to control cancer progression. Further, we uncovered a novel mechanism of angiogenesis modulated by a recently reported class of adhesion molecules. We also completed a clinical study aimed at validating preclinical results.

Benefits for patients
The results obtained in this project have three potential implications:
- *Prognosis/prediction:* The results might allow the identification of patients at risk of developing metastases.
- *Monitoring:* Detected parameters may be used to monitor patients during therapy to evaluate treatment efficacy.
- *Therapy:* Tools generated by this project might translate into new therapeutic approaches to suppress tumour spreading to lymph nodes and to distant sites. Further studies are planned.

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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.–

Cancer stem cells represent an emerging field for cancer research because of the increasing evidence that these cells have the capacity to sustain tumour formation and regeneration. Similar to normal stem cells, cancer stem cells display self-renewing capacity and have the potential to differentiate to a certain extent. Normally, tissue-specific stem cells are implicated in the generation, homeostasis and regeneration of particular organs. In analogy, the cancer stem cell concept predicts that particular cancers arise from specific cancer stem cell types. Unfortunately, cancer stem cells appear to be relatively resistant to radiotherapy and chemotherapy. Thus, it is imperative to better characterize cancer stem cells in order to establish novel therapies specifically targeting these cells.

The skin is the organ with the highest incidence of malignancies, and skin cancers occur more frequently than all other cancers combined. Of the various skin cancers, melanoma is responsible for most deaths. Melanoma cells arise by malignant transformation of melanocytes, the pigment cells in our skin. These cells, in turn, originate during development in the neural crest. In accordance with the hypothesis that melanoma might develop from cancer stem cells, we have identified melanoma stem cells with features of neural crest stem cells. These cells are responsible for both tumour initiation and tumour maintenance.

Intriguingly, we found that factors regulating proliferation and cell survival of normal neural crest stem cells are crucially involved in the initiation and expansion of melanoma: Upon genetic manipulation of such factors in a mouse model of melanoma, neoplastic lesions as well as tumour formation are completely blocked *in vivo*. These findings may help to identify novel targets for the elimination of cancer stem cells. Indeed, we have already identified chemical substances that counteract melanoma stem cell growth and tumour formation in animal models. Our study highlights the importance of collaborative efforts – involving stem cell biologists, pathologists, clinicians, and pharmacologists – for cancer stem cell research and the development of new treatment strategies.

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International Clinical Cancer Research Groups (ICP)

List of completed research groups

Ammann Roland A. et al. | ICP OCS 02061-03-2007 | CHF 118,000.–
Pädiatrische Hämatologie & Onkologie, Universitätsklinik für Kinderheilkunde, Inselspital, Universitätsspital Bern, Bern
International childhood liver tumour consortium – research strategy for treatment and evaluation of hepatoblastoma and hepatocellular carcinoma

Zucca Emanuele et al. | ICP OCS 01356-03-2003 | CHF 983,000.–
Istituto oncologico della Svizzera italiana (IOSI), Ospedale San Giovanni, Bellinzona
International Extranodal Lymphoma Study Group (IELSG): a network for improving the understanding and the clinical management of non-Hodgkin's lymphomas arising at extranodal sites

Ammann Roland A. et al. | **International childhood liver tumour consortium – research strategy for treatment and evaluation of hepatoblastoma and hepatocellular carcinoma**

ICP OCS 02061-03-2007
Duration: 01. 07. 2007 – 30. 06. 2011
CHF 118,000.–

Malignant liver tumours in children are extremely rare. Treatment results have improved considerably in the last 15 years. It has therefore become quite a challenge for treating physicians to choose the correct approach in this rapidly changing field. The Epithelial Liver Tumour Study Group (SIOPEL) of the International Society of Paediatric Oncology (SIOP) has contributed substantially to progress through a programme of clinical studies for treatment of childhood liver cancer. These research studies have led to a significant improvement of both the surgical and chemotherapy treatment. This was rendered possible through the cooperation of over 100 institutions in 32 countries.

In the first two trials, the concept of preoperative chemotherapy was introduced and adapted according to two groups with different prognosis. In the third trial, it was proven that for the patients with operable tumours, the chemotherapy can be reduced to a single agent, thus reducing the potential for possible serious toxicity to the kidneys and cardiac function while achieving excellent long-term survival of over 90 %. For cases with inoperable tumours, chemotherapy was intensified, which led to a high proportion of tumour shrinkage and thus allowed surgical resection, which is indispensable for a complete cure.

SIOPEL has also started an ongoing programme of biomolecular studies in these tumours in order to further adapt the treatment by taking biological parameters into account.

SIOPEL has set up an Internet-based worldwide registry for liver transplantation (Pediatric Liver Unresectable Tumour Observatory, PLUTO) to gather a maximum of information concerning this increasingly popular intervention in case of unresectable tumours. Besides treatment optimization, the group is further investigating molecular biological characteristics and other scientific parameters to be able to include these into better defined risk groups.

SIOPEL has reached an agreement with the Children's Oncology Group (COG, United States), the Society of Paediatric Oncology and Haematology (GPOH, Germany), and the Japanese Study Group for Pediatric Liver Tumor (JPLT, Japan) to merge their study results for a further investigation into possible prognostic factors and defining a strategy for the development of new treatment options.

Statistical support was provided by the Coordinating Center of the International Breast Cancer Study Group (IBCSG, R. Maibach) and the Swiss Group for Clinical Cancer Research (SAKK). The Swiss Paediatric Oncology Group (SPOG) conducts the trials in Switzerland. The central pathology review was done at the Institute of Pathology of the University of Bern. The laboratory of the University Children's Hospital Zurich (M. Grotzer) collects the tissue samples for scientific investigation.

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- Prof. Dr. med. Arthur Zimmermann, Institut für Pathologie, Universität Bern, Bern

Zucca Emanuele et al. | **International Extranodal Lymphoma Study Group (IELSG): a network for improving the understanding and the clinical management of non-Hodgkin's lymphomas arising at extranodal sites**

ICP OCS 01356-03-2003
Duration: 01. 01. 2004 – 31. 12. 2011
CHF 983,000.–

Extranodal lymphomas represent approximately 30–40% of all non-Hodgkin's lymphomas. They develop from all organs and sites of the body, and their clinical history varies significantly depending on the organ of origin. Given the relative low frequency of cases per particular body site, no single institution worldwide would be ever able to accumulate enough cases in order to study the respective clinical history and to establish specific treatment strategies.

The Oncology Institute of Southern Switzerland (IOSI) has been actively involved in this field in the last two decades. 15 years ago, we decided to create the International Extranodal Lymphoma Study Group (IELSG) with the operational office located at the IOSI in Bellinzona. The IELSG is an international cooperative group of institutions that collaborate to perform studies in patients with extranodal lymphomas. The establishment of this group allowed collection of clinical data and biological material of several thousands of extranodal lymphoma cases.

Thanks to this unique worldwide work, the group has developed 35 studies, many of which have been published (see www.ielsg.org). Several other studies are currently ongoing or planned.

Among the most recent contributions of IELSG, in 2011 we published in the most important oncology journal *(Journal of Clinical Oncology)* the results of the IELSG#10 study showing that the prognosis of testicular lymphoma can be improved when proper treatment is given. We also published the results of a study evaluating the role of the proteasome inhibitor Bortezomib in the treatment of marginal zone lymphomas. A case-control epidemiological study (IELSG#13) on the association of viral hepatitis and lymphoma in different European regions was also published by our group.

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Cancer immunotherapy

The hypothesis that certain functions of the immune system prevent the development of cancer was put forward already about 100 years ago, as papers by the German immunology pioneer, Paul Ehrlich, show. In the 1950s it was postulated that the body's surveillance system recognizes and eliminates newly formed cancer cells. Cancer was seen as a rare event in which the tumour cell escaped the efficient control of the immune system. However, this assumption did not hold up to later experimental and clinical studies. It is true that patients treated with medications that suppress the immune system (immunosuppressants) after an organ transplant more frequently develop some types of cancer that originate in white blood cells, namely, lymphoma. But surprisingly, these patients do not have a higher frequency of developing lung cancer, breast cancer or colon cancer. This shows that with solid tumours, immunological surveillance probably does not play the central role as was once supposed.

Immunosurveillance

The immune system can very well influence the progression of cancer. Carcinogenesis is the consequence of various genetic changes that lead to uncontrolled growth and metastasis of cells. As a result of errors that build up in the genetic information of a cell, the gene products of a cancer cell, the proteins, differ from the proteins of the normal cells in number and in structure. These defective proteins can thus be recognized by the immune system as foreign tissue. The prerequisite is that through the aid of certain molecules, an abnormal protein or component of the protein "presents" itself to the defence cells, that is, shows itself and is made accessible. If an antibody, or the receptor of an immune cell, binds to this antigen, an immune reaction is induced. Of special interest to immunotherapy are antigens that are selectively formed only by the tumour and are silent in healthy tissue. They are frequently expressed in structures on the cell surface. Cancer testis (CT) antigens are important representatives of this group. Except for in the testis, they are expressed only in cancerous tissue

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[1]. As healthy testicle tissue does not have any antigen-presenting molecules, the immune response can be directed relatively specifically to the cancer cell.

In experimental animal models, but also when cancer develops in the human body, different mechanisms of the immune system are frequently activated. These include immune cells that kill the body's own cells (cytotoxic T-cells and natural killer cells) and antibodies and white blood cells that eliminate pathogens (granulocytes and macrophages). In many tumour animal models, the main mechanism by which the immune system controls the tumour involves a certain type of white blood cells called $CD8^+$ T-cells. Also human patients with melanoma, ovarian or colon cancer have improved clinical outcome if $CD8^+$ T-cells infiltrate the tumour [2]. But defence by the immune system is in most cases not sufficient to control the cancer. Spontaneous tumour regression that can be attributed mainly to defence by the immune system is rare.

Initial successes after numerous setbacks

Why is immunosurveillance often insufficient? Various mechanisms by which tumours can evade the immune system have been documented [3]. Through an efficient immune response tumour cells are selected that no longer produce the target antigens or that no longer present correctly to the immune cells. These cancer cells are then no longer recognized by the immune system. In addition, the immune response in the tumour is directly inhibited. Regulatory T-cells appear to be particularly important here. They are in the organism naturally, and they suppress the immune response to the body's own antigens as well as the uncontrolled activation of the immune system. They thus prevent autoimmunity, that is, the immune defence of the body's own normal tissue. Patients with tumours show an increased number of regulatory T-cells in the blood and especially in the tumour, where they suppress the anti-tumoural immune response. Clinical studies show that with ovarian cancer, for example, an increased number of regulatory T-cells in the tumour is associated with increased death hazard and reduced survival [4]. In recent years, diverse molecular mechanisms have been discovered that contribute to the suppression or activation of T-cells, which makes new treatment approaches possible.

Immunotherapy has been used in oncology for a long time, even though the mechanisms have not been clarified in detail up to today. An example is local immunotherapy using *Bacillus Calmette-Guérin* (BCG), a weakened tuberculosis bacillus, in the treatment of superficial forms of bladder cancer. Instillation of BCG into the bladder decreases the rate of recurrence most likely through the innate immune system. The "graft versus host effect" after bone marrow transplantation with donor tissue is also based on T-cells and possibly also natural killer cells. For a long time, no significant progress was made in the area of active immunotherapy, and there was often a lack of well-documented clinical studies with large numbers of patients chosen at random to receive the drug treatment or not receive it, under conditions approaching normal practice (randomized phase III trial). In recent years, immunotherapy has definitely moved into everyday clinical practice. The most important advancements in three areas are described in the following.

Passive immunotherapy

Passive immunotherapy is treatment with antibodies or T-cells that are made in the laboratory. Monoclonal antibodies (or mAb) have been used in the treatment of lymphoma and solid tumours for about ten

years. In part these antibodies block certain growth factors in cancer cells or directly trigger their cell death (apoptosis). In addition monoclonal antibodies also activate cells in the immune system, such as macrophages, natural killer cells and granulocytes, which in turn also contribute to the death of the cancer cells. Experimental studies show that with the frequently used antibodies, such as rituximab to treat non-Hodgkin lymphoma, trastuzumab to treat breast and stomach cancer, and cetuximab for colorectal cancer, at least a part of the therapeutic effect is triggered by the immune system [5]. In contrast, passive immunotherapy with T-cells has not been used as a cancer treatment up to now. The problems were the costly production of the specific clones or lines in the lab, their short half-life in patients' bodies and the necessity to produce the T-cells individually due to the need for tissue compatibility. Using gene technology, T-cells were successfully modified to have a two-part receptor to target tumour antigens (chimeric antigen receptor, CAR), which on the one hand recognizes tumour cells and on the other possesses co-stimulation molecules. In initial studies with CAR T-cells, the cancer cells in patients with lymphomas could be completely eliminated [6].

Active immunotherapy

This type of immunotherapy is activation of the body's own immune system through a tumour antigen – comparable to vaccination. The activation can be done by injection of dead cancer cells, purified tumour antigens or small protein fragments of the antigen (peptides). These antigens are injected combined with another substance called an adjuvant that helps boost the immune response even further. This substance facilitates the presentation and thus the visibility of the antigen through dendritic cells, which additionally activates the immune system. Based on increased understanding of the molecular mechanisms by which dendritic cells are activated, various companies have developed more effective adjuvants that are currently being tested in clinical trials. Another possibility is to load dendritic cells with the tumour antigen in the laboratory and to then use the cells as a vaccine. This method is in the most advanced stage of development so far. In 2010 the first large randomized phase II trial was published that showed that active immunization improved survival of patients with metastatic prostate cancer. In this active immunotherapy (treatment with the therapeutic cancer vaccine sipuleucel-T), patients' own dendritic cells are loaded with a tumour antigen in the laboratory [7].

Immunomodulation

In addition to antigen-specific immunotherapy, the immune system can also be activated non-specifically. This mechanism is based mainly on molecules that additionally stimulate or inhibit the immune response. An example is cytotoxic T-lymphocyte antigen 4 (CTLA-4), a protein that is expressed on the surface of T-helper cells and plays an important regulatory role in the immune system. If CTLA-4 binds to a protein called B7 on an antigen-presenting cell, this leads to inhibition of the T-cells. If CTLA-4 is blocked by a monoclonal antibody (for example, ipilimumab), B7 can interact with another protein, the co-stimulator molecule CD28, and the T-cell is activated. Ipilimumab therapy improves the median overall survival of patients with metastatic melanoma by four months [8]. Ipilimumab was the very first therapy to have a significant effect on survival in patients with metastatic melanoma.

It is interesting that the therapy did not lead to visible tumour reduction in computer tomography (CT) scans; in some cases, the tumour was at first even larger. Nevertheless, in the long term the immune system caused stabilization of the cancer. For patients treated with ipilimumab, this non-specific activation of the immune system resulted not only in anti-tumoural immunity but also autoimmunity. This was manifested clinically mainly in symptoms such as diarrhoea, hepatitis, endocrine organs immune-related adverse events and skin-related side effects. Ipilimumab is now being tested with different solid tumours in phase II and phase III clinical trials. Besides the CTLA4-CD28 interaction there are other inhibitory signalling pathways that can be used therapeutically. An important approach already being investigated in studies is suppression of the signal transmission via the T-cell receptor PD-1. The effect on the T-cell is very comparable to the suppression of CTLA-4, and the results of these studies will be available in coming years.

Immune system with a dual role

The positive phase III clinical trials described above are milestones in immunotherapy. As is common in drug development, there were also a large number of negative phase II and phase III studies. However, it was surprising that there were several studies in which immunized patients not only had no benefit from the therapy but also died of cancer sooner than non-immunized control patients did. Some examples are the immunization studies with Canvaxin (the body's own irradiated melanoma cells) or with ganglioside for malignant melanoma. Although not all details have been clarified, researchers assume that in these therapies, certain mechanisms of the immune system, such as regulatory T-cells, were activated that promoted tumour growth. It has been known for a long time that the immune system has a dual role: It can suppress tumour development but can also promote tumour growth. Chronic inflammation, such as in ulcerative colitis, is associated with an increased risk of cancer. The molecular mechanisms that can promote tumour growth are being studied intensively today. These include, for example, cytokines such as tumour necrosis factor α. These proteins transmit signals that regulate the activity of different immune cells.

Recently, our research team found the interaction with the CD27 molecule promotes the development of leukaemia and also the growth of solid tumours [9]. At the same time, however, as a co-stimulatory molecule CD27 can also activate the T-cells. And so the same molecule can improve anti-tumoural immunity in one situation but have the opposite effect in another situation. We need to gain an understanding of the molecular signalling pathways in detail, so that they can be used optimally for treating patients. For this reason, tumour immunology is a prime example of translational research, in which preclinical research in the laboratory works together closely with clinical research with people. With the first positive results reported in the last two or three years, we can expect to see numerous new immunotherapeutic approaches in everyday clinical practice in the future.

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Prof. Adrian Ochsenbein, MD

Adrian Ochsenbein studied medicine at the University of Bern. In 1996 he began his research activity at the Institute of Experimental Immunology at University Hospital Zurich, headed by Nobel Price laureate Prof. Rolf Zinkernagel and Prof. Hans Hengartner. He has worked in medical oncology at the University of Bern since 1999. After completing his Habilitation in 2001 on the mechanisms of the immune response and a subsequent year of postdoctoral research in Seattle, Washington, he was named assistant professor in 2003 and extraordinary professor (Extraordinarius) in 2010 in the Medical Faculty of the University of Bern. Today he is head of the Tumour Immunology Research Group, Department of Clinical Research, University of Bern, and he works at the same time as chief physician at the Institute of Medical Oncology, Bern University Hospital. Ochsenbein is the recipient of many research awards, and he has been a member of the Scientific Committee of the Swiss Cancer League and the Cancer Research Switzerland foundation since 2006.

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List of completed research projects in 2011

Andres Anne-Catherine | KLS 02105-08-2007 | CHF 209,200.–
Departement für klinische Forschung, Universität Bern, Bern
The role of vascularization and tumour stem cells in the metastatic spread of mammary tumour cells: studies in a transgenic mouse model

Detmar Michael | KLS 02182-02-2008 | CHF 330,900.–
Institut für pharmazeutische Wissenschaften, ETH Zürich, Zürich
Lymphatic cancer metastasis: a new therapeutic target

French Lars E. | OCS 02293-08-2008 | CHF 310,300.–
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Studies on the role of inflammasome activation and IL-1 beta in the pathogenesis of melanoma

Heikenwälder Mathias | OCS 02113-08-2007 | CHF 317,450.–
Institut für Neuropathologie, UniversitätsSpital Zürich, Zürich
Molecular dissection of hepatocellular carcinogenesis in mice with chronic hepatitis, a mouse model of hepatitis-associated human hepatocellular carcinoma

Hübscher Ulrich | KLS 02339-02-2009 | CHF 203,100.–
Institut für Veterinärbiochemie und Molekularbiologie, Universität Zürich, Zürich
Regulation of base excision repair by human DNA polymerase lambda through posttranslational modification: degradation versus stabilization

Janscak Pavel | KLS 02344-02-2009 | CHF 74,800.–
Institut für molekulare Krebsforschung, Universität Zürich, Zürich
Study of the role of mismatch repair proteins in the cellular response to DNA double-strand breaks

Manz Markus G. | OCS 02019-02-2007 | CHF 196,500.–
Klinik für Hämatologie, UniversitätsSpital Zürich, Zürich
An in vivo study on the stem cell origin of chronic myeloproliferative disorders

Matthias Patrick | OCS 02177-02-2008 | CHF 92,500.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Role of the deacetylases HDAC1 and 2 for cell cycle progression in normal and cancer settings

Meraldi Patrick | KLS 02185-02-2008 | CHF 234,100.–
Institut für Biochemie, ETH Zürich, Zürich
Investigating the role of the spindle checkpoint protein Bub1 in cancer formation

Petrova Tatiana | OCS 02263-08-2008 | CHF 399,400.–
Division d'oncologie expérimentale, Centre pluridisciplinaire d'oncologie (CePO),
Centre hospitalier universitaire vaudois (CHUV) et Université de Lausanne, Epalinges
The role of the transcription factor Prox1 in colon and lung tumourigenesis

Plückthun Andreas | KFS 02448-08-2009 | CHF 238,600.–
Biochemisches Institut, Universität Zürich, Zürich
Tumour targeting of ErbB2 with designed ankyrin repeat proteins

Scorrano Luca | OCS 02213-02-2008 | CHF 353,200.–
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Exploring the role of mitochondria-shaping proteins in apoptosis: novel therapeutic targets to drive death of cancer cells

Sommer Lukas | OCS 02256-08-2008 | CHF 338,400.–
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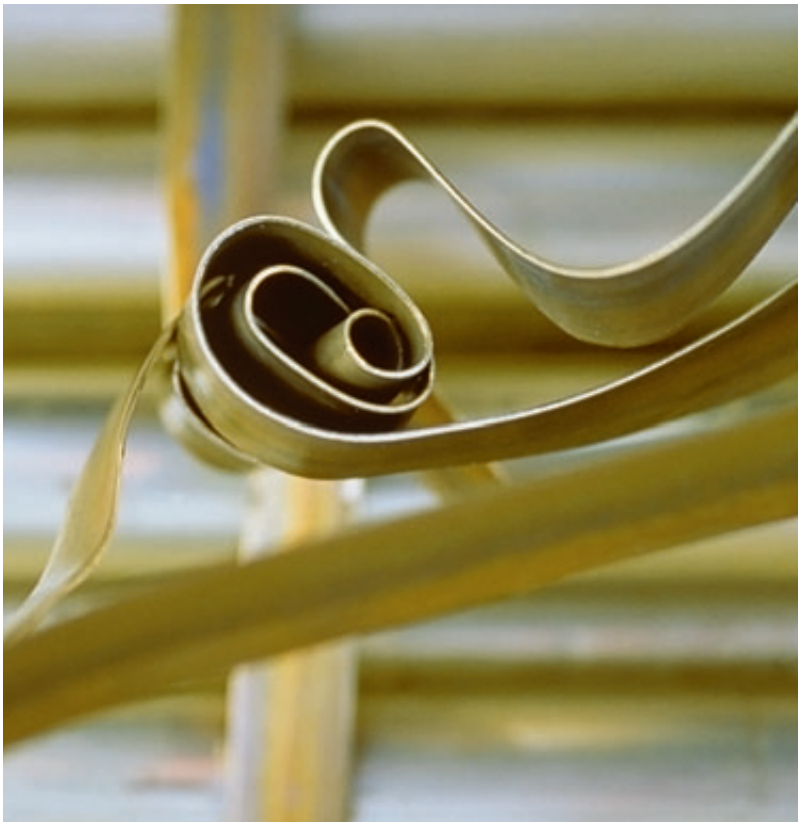
Neural crest development and cancer – the role of neural crest stem cell-like melanoma cells in metastasis



Stamenkovic Ivan | OCS 02158-02-2008 | CHF 255,800.–
Institut universitaire de pathologie de Lausanne (IUP), Université de Lausanne, Lausanne
Analysis of the molecular mechanisms underlying the pathogenesis of Ewing's family tumours

Swartz Melody | OCS 02114-08-2007 | CHF 339,450.–
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Roles of CCR7 and VEGF-C in lymphatic metastasis of breast and skin cancer

Wicki Andreas | OCS 02102-08-2007 | CHF 305,400.–
Medizinische Onkologie, Universitätsspital Basel, Basel
Mechanisms of tumour progression upon dissolution of adherens junctions

Zaugg Kathrin | KLS 02569-02-2010 | CHF 78,000.–
Klinik für Radio-Onkologie, UniversitätsSpital Zürich, Zürich
Elucidating the role of the hypoxia-protective gene CPT1C (carnitine palmitoyl-transferase 1C) in carcinogenesis

Presentation of completed research projects in 2011

Andres Anne-Catherine | **The role of vascularization and tumour stem cells in the metastatic spread of mammary tumour cells: studies in a transgenic mouse model** (KLS 02105-08-2007)

Breast cancer is one of the most frequent malignancies in the Western world. The burden of this disease with still frequent lethal outcome is not the primary tumour itself but the metastases developing thereof. Thus, it is important to understand the mechanisms allowing tumour cells to metastasize in order to develop efficient treatment strategies. The cancer stem cell theory implies that cancerous tissues show a hierarchy similar to normal tissues, i.e., they are composed of stem cells and their differentiating descendants. Moreover, it is thought that only the rare cancer stem cells are in fact responsible for relapse and metastasis formation. The EphB4 receptor and its membrane-bound ligand ephrin-B2 play a key role during embryogenesis, in the maintenance of adult organ structure, and in the control of regenerative progenitor cells, a cell population that is of primary importance for the continuous cyclic development of the mammary gland.

To elucidate the function of EphB4 and ephrin-B2 in the growth control of the mammary epithelium we established transgenic mice exhibiting overexpression of the EphB4 receptor or the ephrin-B2 ligand as well as of a dominant negative ligand mutant in the mammary epithelium. With these transgenic mouse models we found that the deregulated expression of these molecules leads to a disturbed development of the mammary parenchyma and vasculature. In particular, overexpression of the EphB4 receptor as well as the inhibition of the ephrin-B2 ligand conferred a metastatic phenotype on sessile tumour cells. In contrast to non-metastasizing tumours, these carcinomas exhibited a high number of cells with stem cell characteristics.

We therefore analysed the impact of ephrin-B2 inactivation on the homeostasis and differentiation pathway of the stem cells in the normal tissue. We could show that the inactivation of ephrin-B2 resulted in an augmentation of the stem cell population and to a shift of the differentiation pathway towards the estrogen receptor positive sensory cells. These results suggest that this expanding stem cell population represents the origin of the metastatic carcinogenic growth. Thus, the inactivation of ephrin-B2 leads to a deregulation of the mammary stem cell niche and thereby contributes to the metastatic potential long before carcinogenic growth becomes apparent.

With our research efforts we not only strengthen the cancer stem cell hypothesis and demonstrate the important role of Eph and ephrin signalling in the control of the breast epithelium but also contribute to the development of new treatment strategies.

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Detmar Michael | **Lymphatic cancer metastasis: a new therapeutic target** (KLS 02182-02-2008)

Tumour metastasis to the draining (sentinel) lymph nodes represents the first step of metastatic tumour dissemination in the majority of human cancers. Lymph node metastasis indeed serves as an important prognostic indicator in cancer patients, with important implications for the choice of therapy. In 2001 we and others discovered a novel mechanism of cancer metastasis by which primary cancers induce lymphatic vessel growth, leading to increased metastasis to the draining lymph nodes and to distant organs. In our recent studies in experimental metastasis models, we have discovered that tumours (by secretion of specific growth factors) also induce lymphangiogenesis (growth of lymphatic vessels) in their draining lymph nodes even before they metastasize, leading to increased cancer spread to distal lymph nodes and organs. This mechanism has also been found in human cancers, in particular in breast cancer and in malignant melanoma. Therefore, tumour-induced lymphatic vessel activation represents a promising new target to prevent or treat metastatic cancer.

In this project, we studied the molecular mechanisms mediating tumour lymphangiogenesis and lymphatic cancer spread, and identified new targets for anti-metastatic therapies by inhibition of tumour and lymph node lymphangiogenesis. To this end, we studied the differences in gene activity between tumour-activated lymphatic endothelium and lymphatic endothelium in normal tissue. We isolated the lymphatic endothelium from the tissues, using a new method that we developed named “immuno laser capture microdissection”. For this, the lymphatic vessels in tissue sections are stained by a very rapid method, and then a laser beam is used to cut out the cells from tissue sections. We studied, by gene arrays, the activity of approximately 20,000 genes.

We found several genes that were more active in tumour-induced lymphatic vessels than in normal lymphatic vessels. It is of interest that some of these genes play important roles in the growth of new lymphatic vessels. We confirmed the activity in cell cultures of lymphatic endothelial cells. One factor named neuropilin-2 is of particular interest, since it is a receptor for growth factors that activate the lymphatic endothelium. We will now use antibodies that block the function of neuropilin-2 to treat cancer growth and metastasis in experimental cancer models.

We anticipate that treatment with the neuropilin-2 antibody will inhibit the metastatic spread of cancer cells and will therefore represent a novel strategy for anti-cancer therapies. Importantly, based on the new method of "immuno laser capture microdissection" that we developed in this project, we have now been able to isolate tumour vessels also directly from human cancers. These studies have revealed additional molecules that are more strongly expressed in human cancer vessels and that could be used as new targets for therapy.

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French Lars E. | **Studies on the role of inflammasome activation and IL-1 beta in the pathogenesis of melanoma** (OCS 02293-08-2008)

Chronic inflammation has been reported to play a significant role in cancer development. IL-1b is a very potent pro-inflammatory cytokine that has been suggested to be involved in melanoma pathogenesis. However, the source of IL-1b in tumours remains very controversial.

In our project, we showed that melanoma cells taken from either primary cutaneous tumours or metastases are not able to produce IL-1b *in vitro*. Therefore, a possible source of IL-1b in the tumour microenvironment could be infiltrating antigen presenting cells such as dendritic cells (DCs). Indeed, there is evidence that there is an interaction between tumour cells and cells of the innate immunity. However, the danger signals triggering DC activation and subsequent IL-1b release remain unknown. Since necrotic areas often develop within growing melanoma lesions, we addressed the question as to whether necrotic cells could release danger signals and subsequently activate DCs and induce IL-1b secretion. The incubation of necrotic melanoma cells *in vitro* with monocytes or DCs resulted in high levels of IL-1b release. We therefore focussed on the identification of the molecules present in the necrotic cell fraction that could trigger pro-inflammatory cytokine secretion. High mobility group box-1 (HMGB1) protein is a DNA-binding protein involved in gene expression and chromatin remodelling, which additionally to its nuclear expression is released into the extracellular space upon cell stress and damage. HMGB1 has been identified as a key molecule linking tissue damage and stress to activation of innate immune mechanisms and is considered to be a danger associated molecule or alarmin. We showed that HMGB1 can be found at high levels in necrotic melanoma cells.

Functional experiments using cells in which HMGB1 has been silenced are ongoing to clearly define the role of this protein as a danger signal in the necrotic areas of melanoma.

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Heikenwälder Mathias | **Molecular dissection of hepatocellular carcinogenesis in mice with chronic hepatitis, a mouse model of hepatitis-associated human hepatocellular carcinoma**
(OCS 02113-08-2007)

In this study, we analysed liver-needle biopsies of patients who had developed hepatocellular carcinoma (HCC) as a consequence of chronic inflammatory or non-inflammatory liver diseases. We identified a particular signalling pathway, the lymphotoxin signalling pathway, which appeared activated in patients with chronic Hepatitis B and C (HBV; HCV) or patients that had developed HCC as a consequence of HBV or HCV infection.

Consequently, we generated transgenic mice to investigate whether upregulation of the lymphotoxin signalling pathway was causally or correlatively linked to HCC development. Indeed, lymphotoxin expression specifically in hepatocytes of mice (AlbLTab) sufficed to induce inflammation-driven HCC. We analysed HCC on genetic, biochemical, and immunohistological levels and found that HCC are capable of metastasizing intrahepatically.

The mechanism responsible for HCC development in AlbLTab mice was linked to enhanced NFκB signalling within hepatocytes and the presence of lymphocytes but independent of tumour necrosis factor receptor 1 (TNFR1) and 2 signalling. Treatment with soluble lymphotoxin receptor (LTβR-Ig) abrogated hepatitis and liver cancer development. In addition to this study, we found that a signalling molecule that belongs to the NFκB signalling pathway controls development of aggressive liver cancer.

Aim
The aim of this study was to analyse the molecular and cellular pathways of inflammation-induced liver cancer in a mouse model. Further on, this mouse model was used to investigate novel anti-inflammatory and anti-cancer therapies.

Method and procedure
We analysed liver-needle biopsies of patients who had developed hepatocellular carcinoma (HCC) as a consequence of chronic inflammatory or non-inflammatory liver diseases for the expression of genes of the tumour necrosis factor (TNF) superfamily. Further, we isolated liver tissue from curative re-sectios with HCV-induced HCC in order to isolate parenchymal and non-parenchymal cells for the expression of lymphotoxin (LT) and other members of the TNF superfamily of the affected and unaffected liver. Moreover, we generated transgenic mice expressing LTα and LTβ) specifically on hepatocytes (AlbLTab) and analysed them biochemically (e.g., Western-blot; Real-time PCR; ELISA), immunohistochemically, and by flow cytometry (FACS). Finally, backcrossing experiments were performed with $Rag2^{-/-}$, $IKKb^{Dhep}$, $TNFR1^{-/-}$, and $TNFR2^{-/-}$ mice to dissect the cells and signalling pathways leading to cancer.

Study results
We found that the upregulation of LT and the activation of the LTβR signalling pathway are causally linked to development of hepatitis and liver cancer. The mechanism responsible for HCC development in AlbLTab mice was linked to enhanced NFκB signalling within hepatocytes and the presence of lymphocytes but independent of TNF receptor 1 (TNFR1) and 2 signalling. Treatment with soluble lymphotoxin receptor (LTβR-Ig) abrogated hepatitis and liver cancer development. In addition to this study, we found that a signalling molecule that belongs to the NFκB signalling pathway controls development of aggressive liver cancer.

Potential benefit for patients
Treatment with soluble lymphotoxin receptor (LTβR-Ig) might become an efficient therapy to treat chronic virus-induced hepatitis and liver cancer.

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Hübscher Ulrich | **Regulation of base excision repair by human DNA polymerase lambda through posttranslational modification: degradation versus stabilisation** (KLS 02339-02-2009)

Oxygen is necessary for life. But besides being an absolutely necessary component for life, it can also have a deleterious effect. Charged oxygen molecules are very reactive and can change vital functions in the body. This is called oxidative stress, which is responsible for many diseases in humans and animals and especially for the development of cancer. When the body gets too much oxidative stress, it can develop diseases. Oxidative stress can derive from inside the body by oxidative phosphorylation in the mitochondria and from outside by ultraviolet light, x-ray, toxins in the environment, smoking, and alcohol abuse. If this stress is constantly high, the body can no longer handle the oxidative burden and the destructive potential of the oxygen radicals can lead to diseases.

In collaboration with a research group in Oxford (England) we found and characterised a regulatory pathway of DNA repair that can handle thousands of lesions in a single cell in the DNA caused by oxidative damage every day. One of the most dangerous types of damage is oxidation of the guanine bases in DNA, leading to the oxidation product 8-Oxoguanine. We found further that the regulation has to be controlled at the right time and at the right place.

What are the consequences of our findings? A big clinical study in 2007 showed that important cancers such as lung, breast, stomach, ovary, and colon cancers are the consequence of insufficient DNA repair of oxidative damage. We are currently collaborating with clinicians from University Hospital Zurich and Vetsuisse Hospital Zurich to find out whether regulatory pathways in the above-mentioned cancers are misregulated.

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Janscak Pavel | **Study of the role of mismatch repair proteins in the cellular response to DNA double-strand breaks** (KLS 02344-02-2009)

DNA damage is a frequent event in the life of a cell. Failure to repair DNA damage can lead to cell death, while inaccurate DNA repair can give rise to genomic instability, which promotes the onset of cancer in mammals. The most deleterious form of DNA damage is DNA double-strand break (DSB). In eukaryotic cells, two mechanistically distinct pathways are known to efficiently repair DSBs: non-homologous end joining and homologous recombination (HR). However, molecular mechanisms underlying these DNA repair pathways are not completely understood. Previous studies in yeast and human cells revealed that proteins involved in the initiation of post-replicative mismatch repair (MMR), such as MSH2, MSH3, MSH6, and MLH1, accumulate at the sites of chromosomal DSBs. The goal of this project was to explore the possible role of MMR proteins in DSB signalling and repair.

The project utilized various cell biology and biochemistry methods in combination with laser micro-dissection technology and immunofluorescence microscopy. We established laser microirradiation technique to generate DSBs in defined, spatially restricted nuclear volumes. By immunofluorescence microscopy, we observed that MMR proteins rapidly re-localized to laser-irradiated nuclear areas in a wide variety of human cell lines. Moreover, using siRNA technology and mutant cell lines, we found that the MMR were recruited to DSBs during presynaptic stage of HR in a manner dependent on CtIP and MRE11 that are required for DSB resection, the initial step of HR. Furthermore, we discovered that MSH2 and MSH3, but not MSH6 and MLH1, were required for RPA phosphorylation in response to replication-associated DSBs induced by the topoisomerase I inhibitor camptothecin. In addition, we found that lack of MSH2 or MSH3 caused impairment of HR-mediated DSB repair in human cells. Finally, using purified proteins, we demonstrated that the MSH2/MSH3 heterodimer was bound specifically to complexes of RPA with single-stranded DNA (ssDNA), which are formed following DSB resection. Together, these findings suggest that the MSH2/MSH3 heterodimer operates on RPA-coated ssDNA following DSB resection to facilitate ATR-dependent RPA phosphorylation that is required for efficient DNA repair by HR.

Germline mutations in the MLH1, MSH2, and MSH6 genes are the major cause of hereditary non-polyposis colon cancer. Our findings have implications for understanding the molecular events leading to this most common form of inherited colon cancer.

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Matthias Patrick | **Role of the deacetylases HDAC1 and 2 for cell cycle progression in normal and cancer settings** (OCS 02177-02-2008)

Histone deacetylases (HDACs) inhibitors represent a new class of therapeutic substances that are active in a range of pathologic conditions such as cancer and neurodegenerative or autoimmune diseases. These substances are considered very promising, and two have recently been approved for the treatment of a specific lymphoma type. The human genome contains 11 HDAC enzymes, and it is unknown to what extent these enzymes have specific and/or redundant functions – either in normal or pathological situations. The current inhibitors inhibit all HDACs without discrimination and have significant side effects. In the hope of eventually improving current therapies, and also developing new therapies, it is paramount to better understand the role of individual HDACs in physiological and pathological regulation.

To this end we are analysing the two main HDACs, HDAC1 and HDAC2. As a model system we are using mouse B-lymphocytes, which are the cells producing antibodies. The goal of our project was to determine the role of these two enzymes in the development and proliferation of B-cells.

Our studies showed that at the minimum one of these enzymes – HDAC1 or HDAC2 – is required for the normal development of B-cells. In the absence of both enzymes, B-cell development is arrested at an early stage, and the cells are blocked in the cell cycle. These results are important, as they demonstrate that the elimination – or the pharmaceutical inhibition – of HDAC1 and HDAC2 is sufficient to block the proliferation of normal cells. It remains to be seen whether the same result can be obtained with cancer cells, and we are currently testing this hypothesis with a B-cell lymphoma model.

If the outcome of these experiments is positive, it will indicate that inhibitors specific for HDAC1 and HDAC2 would be therapeutically interesting, as they would likely have fewer side effects than the pan-inhibitors currently used.

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Meraldi Patrick | **Investigating the role of the spindle checkpoint protein Bub1 in cancer formation** (KLS 02185-02-2008)

When cells divide, each daughter cell has to inherit two copies of every chromosome to ensure the correct propagation of all genetic information. This is achieved by the mitotic spindle, which binds the chromosomes, aligns them in the middle of the cell (so-called metaphase), and distributes them to both sides of the dividing cell. Errors in this process are frequent in tumours, as cells in 85% of solid human cancers show an imbalance in the number of chromosomes (whereas normal cells contain two copies of every chromosome, cancer cells contain either more than two or only one copy of certain chromosomes). These imbalances are not only a symptom of cancers; they are also a potential cause, since chromosomal imbalances are sufficient to induce cancer in mice.

One interesting enzyme that has emerged in this process is the protein kinase Bub1 (kinases are enzymes that phosphorylate other proteins). Bub1 was known to play two roles during cell division: First, it is part of the spindle checkpoint, a control mechanism ensuring that cells do not finish their division as long as the mitotic spindle has not bound all the chromosomes; second it is required for the alignment of the chromosomes in the middle of the cells. Finally, Bub1 mutations have been found in cancer cells; however, their significance was unknown.

Aim of the study
Our aim was to better understand how Bub1 can control two different functions during cell division, and to investigate whether cancer-associated Bub1 mutations impair the correct repartition of chromosomes.

Method
Using cell biological tools we replaced the normal Bub1 present in the cells with different mutants and studied their impact on cell division by microscopy. The mutants included Bub1 kinase missing different segments of the protein, mutants with an impaired kinase activity, or Bub1 mutants specifically found in cancer cells. These studies were carried out in cancer cells and normal non-cancerous cells.

Results
We found that the different functions of Bub1 are controlled by different segments of the protein: The kinase activity is essential for chromosome alignment but is not required for the spindle checkpoint control mechanism. In contrast, a small central part of Bub1 was shown to be essential for the spindle checkpoint but to play no role in chromosome alignment. Interestingly, the mutants of Bub1 found in cancer cells also led to defects in both chromosome alignment and spindle checkpoint, suggesting that such mutants could play a role in the origin of these cancers.

Potential benefit of the study
This highlights the importance of Bub1 during cell division and identifies several Bub1 mutants as possible players in cancer formation, a finding that may be important for more precise differentiation and diagnostics of cancers in patients.

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Petrova Tatiana | **The role of the transcription factor Prox1 in colon and lung tumourigenesis**
(OCS 02263-08-2008)

Colon and lung cancers are among the most common cancer types in the world. Whereas the mechanisms of cancer initiation are beginning to be understood, developing efficient therapies requires better knowledge of molecular regulators of cancer progression. We showed previously that the transcription factor Prox1 is overexpressed in colon adenomas and adenocarcinomas and that Prox1 contributes to tumour progression.

The objective of this study was to uncover the molecular mechanisms of Prox1 in late stage colon cancers in order to identify Prox1 target genes and pathways, as well as to analyse a potential role of Prox1 in lung cancer. To answer these questions we carried out analysis of Prox1 DNA binding sites, using next generation sequencing approaches, and we analysed genes regulated by this transcription factor in colon and lung cancer cells. We also studied whether in addition to its role at early stages of colon cancer development Prox1 plays a role in tumour dissemination.

We found that Prox1 is a part of the TCF/β-catenin transcriptional complex in cultured colon cancer cells, mouse intestinal epithelial cells with activated Wnt signalling and human colon adenocarcinomas. To understand the mechanism of Prox1 action, we interrogated the genome of colon cancer cells for Prox1, TCF4 (TCF7L2) and β-catenin binding sites, and we showed that TCF4, β-catenin and Prox1 simultaneously bind to a subset of genomic enhancers on which Prox1 acts as a transcriptional repressor.

These results suggest that Prox1 is a colon-cancer specific modifier of TCF/β-catenin signal transduction pathway. We propose that this is one of the mechanisms by which sustained Wnt signalling, observed in the majority of colon cancers, transforms an initially normal intestinal progenitor program into a cancer-specific output that will later contribute to unrestricted tumour growth, invasion and dissemination.

Our results in orthotopic colon cancer models further demonstrated that in advanced cancers, Prox1 is dispensable for primary tumour growth, while it is important for tumour spread to distant organs. The work on lung cancer is still in progress, but we observed a similar role of Prox1 in the development of a subset of lung cancers using tumour xenograft approaches. Our results provide a basis for identification of direct Prox1 target genes and suggest that targeting Prox1 transcriptional network should be investigated as a strategy to prevent growth of colon cancer metastasis.

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Plückthun Andreas | **Tumour targeting of ErbB2 with designed ankyrin repeat proteins**
(KFS 02448-08-2009)

Tumour targeting, which has been promoted by technological advances in molecular biomedicine, has contributed substantially to the improvement of efficacy and personalization of tumour therapy over the last years. Tumour targeting vehicles, such as antibodies, allow cytostatic drugs or an immune response to act directly on the site of the tumour. Nevertheless, the currently used targeting molecules often suffer from limited efficacy, unfavourable biophysical properties, and expensive production. Therefore, complementary molecular scaffolds are highly needed and are being intensely searched for. We have developed a new class of binding molecules, termed

"designed ankyrin repeat proteins" (DARPins) that display outstanding stability, specificity as well as versatility, and high affinities for their targets, and they can be manufactured in large amounts at low cost in bacteria.

We have chosen the ErbB2 receptor as a target tumour antigen. Overexpression of ErbB2 occurs in a broad range of human cancers, including up to 30 % of breast carcinoma, and high ErbB2 levels have been correlated with an aggressive metastatic tumour phenotype. High expression of ErbB2 may be thus employed for tumour targeting, where the receptor is used as a cellular gate to convey therapeutic payloads into the tumour cells. In some cases, the inhibition of tumour growth may be induced solely by the binding to the receptor, thereby impairing its function, inasmuch as ErbB2 is required for the proliferation of tumour cells. To achieve high treatment efficiency, we aimed to construct targeting molecules combining several favourable attributes.

By employing state-of-the-art biotechnology procedures, a number of ErbB2-directed binders were selected and profiled for their efficiency to inhibit tumour growth in cell culture models. The resulting molecules reached anti-tumour activity that surpassed the efficacy of the therapeutic antibodies currently used in the clinic. In contrast to tumouristatic antibodies known to induce growth arrest of tumour cells, the high tumouricidal activity of DARPins was attributable to an additional, potent induction of cell death (apoptosis) of the treated cells. In fact, we demonstrated that DARPins downregulate several cell signalling pathways governing cell growth and survival of tumour cells.

Due to the high specificity and absence of any cytotoxic additives or moieties, these anti-tumour DARPins, despite their potency, are expected to be devoid of adverse side effects. This property will translate into high therapeutic benefit in the clinical treatment. Recent studies in animal models confirmed that DARPins are well tolerated, accumulate to high titers on the engrafted tumours, and, consequently, inhibit efficiently the growth of tumour cells *in vivo*. Thus, owing to their strong and utmost specific tumouricidal activity, these novel substances are envisaged as prospective anti-tumour agents in a number of therapeutic applications, in particular in the treatment of breast cancer.

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Sommer Lukas | **Neural crest development and cancer: the role of neural crest stem cell-like melanoma cells in metastasis** (OCS 02256-08-2008)

Metastatic melanoma represents one of the most fatal skin tumours in industrialized countries. To establish more effective therapies, the mechanisms underlying dissemination of metastasizing melanoma cells have to be elucidated. Because melanoma results from transformation of neural crest-derived melanocytes, processes implicated in neural crest cell dissemination and migration during embryonic development might also be relevant during melanoma formation. In particular, neural crest cells delaminate from the embryonic neural tube by undergoing an epithelial-to-mesenchymal transition (EMT), a process also implicated in early steps of tumour metastasis. To address whether mechanisms involved in neural crest cell EMT and migration play a role in aggressive melanoma, new research models closely resembling the human disease are required.

Therefore, we established a novel model system for human melanoma that faithfully recapitulates the early steps of human melanoma metastasis, including disease initiation and tissue invasion. In this system, human skin substitutes are engineered from human keratinocytes and dermal cells, and human melanoma cells are then seeded into such skin substitutes. Transplantation of the skin substitutes on to the back of immunocompromised rats consistently results in development of melanoma displaying the hallmarks of the patients' tumours. Importantly, all initial steps of disease progression are recapitulated, including the incorporation of the tumour cells into their physiological microenvironment at the basement membrane, transition of radial to vertical growth, and establishment of highly vascularized, aggressive tumours in deep-lying skin structures. Of note, processes also found during neural crest EMT appear to take place at early stages of tumourigenesis in this model, such as basement membrane disruption and E-Cadherin downregulation in disseminating tumour cells. Because all cellular components (i.e., human melanoma cells, keratinocytes, and dermal fibroblasts) can be individually manipulated using our approach, it provides a means to dissect tumour cell autonomous and non-autonomous pathways regulating human disease progression. Indeed, manipulation of known neural crest EMT signalling pathways influence invasiveness and growth of human melanoma cells in our model system.

The knowledge of how different steps of melanoma metastasis are controlled might help to identify new targets for therapy.

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Swartz Melody | **Roles of CCR7 and VEGF-C in lymphatic metastasis of breast and skin cancer**
(OCS 02114-08-2007)

Many cancers metastasize – or invade an organ distant from their primary site – via the lymphatic system. Little is known, however, about the initial steps of metastasis, e.g., the homing of cancer cells to lymphatic vessels, their subsequent entry and transport within the lymphatic system, and their interactions within the sentinel draining lymph node (dLN). In this project, we examined the mechanisms underlying the invasion and homing of tumour cells through the extracellular matrix towards the draining lymphatic vessels, with special emphases on the biomechanical environment (i.e., interstitial flow directed from the tumour towards the draining lymphatic vessel) and the cross-talk between two known mediators of lymphatic metastasis: the lymphatic growth factor VEGF-C (and its receptor VEGFR-3) and the lymphoid homing chemokine CCL21 (whose receptor, CCR7, is normally expressed by migrating immune cells). We developed and characterized *in vitro* tools and methods to study chemokine signalling and interstitial flow on tumour cell migration. We then turned to *in vivo* models of melanoma, where we studied the effect of chemokines and flow on tumour invasion, tumour cell-stromal cell interactions, and tumour-induced immune tolerance in the tumour and dLN.

In Issa et al. (*Cancer Res.* 2009; 69: 349–57), we showed that VEGF-C overexpression by melanoma cells enhanced their proteolysis, invasiveness, and chemoinvasion towards lymphatic endothelial cells (LECs) in a manner dependent on both CCL21/CCR7 and VEGF-C/VEGFR-3, thus bridging the known pro-metastatic functions of these factors in tumours for the first time. In Shieh et al. (*Cancer Res.* 2011; 71(3): 790–800), we found that interstitial flow synergistically enhanced tumour cell invasion by fibroblasts through a mechanism of matrix priming. This novel mechanism promoted the concept that interstitial flow is an important pro-tumour component of the stromal microenvironment. In Shields et al. (*Science,* 2010; 328(5979): 749–52), we showed that naturally occurring levels of CCL21 by mouse melanomas are sufficient to drive the transformation of the tumour stroma to mimic that of the lymph node, which together with tolerogenic chemokines secreted by the tumour, can promote host immune tolerance to the tumour. Finally, in Lund et al. (*Cell Reports,* 2012; 1(3): 191–99), we demonstrated that tumour VEGF-C promotes immune tolerance by driving regulatory changes in the tumour stroma and dLN, and by causing the deletion of tumour-specific cytotoxic T-cells by VEGF-C-stimulated LECs. Importantly, VEGF-C protected tumours against pre-existing anti-tumour immunity and could be explained by the cross-presentation of exogenous antigen by LECs in the dLN.

The work we were able to carry out with the funding of Oncosuisse brought us from our initial hypothesis – that cross-talk between CCL21 and VEGF-C was important in lymphatic metastasis of tumours – to a new paradigm identifying the immune system as a central mechanism underlying this cross-talk. We propose that VEGF-C and tumour-associated lymphatics promote immune tolerance and may therefore be a novel target for immunotherapeutic intervention. Moreover, chemokine-induced lymph node mimicry as a mechanism for immune tolerance opens up new strategic targets for cancer immunotherapy, including targeting the lymphatic system, as well as modalities for overcoming tolerance in autoimmune diseases.

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Wicki Andreas | **Mechanisms of tumour progression upon dissolution of adherens junctions**
(OCS 02102-08-2007)

One in three people will suffer from cancer during their lifetime. The serious consequences of a malignant disease do not usually result from the primary tumour but from the formation of metastasis. Therefore, it is important to understand the mechanisms that underlie the process of tumour invasion and the migration of tumour cells into different organs.

Tumour cells can invade through two distinct pathways: They can either migrate as a large cell sheet and intravasate as a tightly linked group of cells (collective invasion), or they can lose adhesive properties and invade the tissue as single cells (single cell invasion). To move as single cells, tumour cells must downregulate adhesive molecules and undergo a process termed epithelial-mesenchymal transition (EMT).

Cadherins are important components of cell junctions. Their function is calcium-dependent and results in a tight adhesive structure between two or more cells. Intracellularly, these adhesive proteins are linked to the cytoskeleton by the means of catenins. In our project, we genetically knocked out E-cadherin, betacatenin, or p120 catenin in a mouse model of human cancer and investigated side by side the effect of these knockouts on tumour invasion and metastasis.

Our experiments showed that losing adhesive cell junctions through knockout of E-cadherin results in single cell invasion and metastasis at a very early stage of tumour formation. Interestingly, this was not the case upon knockdown of catenins, in particular beta-catenin. Apparently, to a certain extent the catenins are redundant and can

compensate for the loss of one member of the catenin family. We also addressed the question which intracellular signals are altered due to the loss of cell adhesion. Importantly, we could not confirm the hypothesis that Wnt signalling is upregulated upon loss of E-cadherin. Rather, there appears to be signalling at the level of the cytoskeleton that influences cell motility.

We know from clinical oncology that tumours are very artful in circumventing the effect of anti-cancer drugs. Changing from collective to single cell invasion and vice versa is one of the crucial mechanisms. Current anti-cancer strategies are aimed at killing cancer cells; pharmacological compounds that target cell invasion or migration and thus metastasis formation are lacking. This is a major problem, since we and others showed that metastasis is an early and continuing process that needs to be addressed separately from the question of eliminating tumour cells. A deeper understanding of the pathways involved in cell invasion and metastasis will ultimately lead to more effective cancer therapy.

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Zaugg Kathrin | **Elucidating the role of the hypoxia-protective gene CPT1C (carnitine palmitoyl-transferase 1C) in carcinogenesis** (KLS 02569-02-2010)

Our lab is interested in using the discriminating characteristics of the tumour cell as a platform for designing novel therapies. Tolerance of chronic low oxygen environments, also known as hypoxia tolerance, is a major distinguishing characteristic of the tumour cell in the body. Hand in hand with hypoxia tolerance is an alteration of the metabolism of the tumour cell, whereby most of the energy to feed the growth of the cell comes from alternate sources. It is our belief that increased efforts at understanding and intervening with the pathway(s) leading to hypoxia tolerance will provide anti-cancer therapies both on their own and in combination with radiotherapy.

Our previous research led to the identification of CPT1C (carnitine palmitoyltransferase 1C) as a novel p53 target gene *in vitro* and *in vivo*. CPT family members regulate the transport of free fatty acids into the mitochondria, where they get access to beta-oxidation. Loss-of-function of CPT1C was generated in mouse embryonic stem cells ($CPT1C^{gt/gt}$ ES cells). Importantly, $CPT1C^{gt/gt}$ ES cells readily succumbed to cell death under hypoxic conditions, whereas control cells were resistant. Using transient knock-down models for CPT1C, the same striking *in vitro* effect was found in different human cancer cell lines (*Genes & Development,* 2011). Furthermore, using a murine tumour model (NF1/p53 heterozygous mice), we found that loss of CPT1C leads to a significant increase of survival of these mice, strongly supporting our hypothesis that CPT1C plays a key role in carcinogenesis. The mechanism of action by which CPT1C protects cancer cells from hypoxia is currently under investigation in our laboratory.

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Further completed research projects in 2011

Manz Markus G. | OCS 02019-02-2007 | CHF 196,500.–
Klinik für Hämatologie, UniversitätsSpital Zürich, Zürich
An in vivo study on the stem cell origin of chronic myeloproliferative disorders

Scorrano Luca | OCS 02213-02-2008 | CHF 353,200.–
Département de physiologie cellulaire et métabolisme, Centre médical universitaire (CMU), Université de Genève, Genève
Exploring the role of mitochondria-shaping proteins in apoptosis: novel therapeutic targets to drive death of cancer cells

Stamenkovic Ivan | OCS 02158-02-2008 | CHF 255,800.–
Institut universitaire de pathologie de Lausanne (IUP), Université de Lausanne, Lausanne
Analysis of the molecular mechanisms underlying the pathogenesis of Ewing's family tumours

Basic biomedical research

List of approved research projects in 2011

Total funds allocated: CHF 7,558,400.–

Andres Anne-Catherine | KLS 02825-08-2011 | CHF 114,000.–
Departement für klinische Forschung, Universität Bern, Bern
The molecular mechanisms provoking the ephrin-B2 induced deregulation of the mammary stem cell niche and leading to metastatic tumour growth

Basler Konrad | KFS 02749-02-2011 | CHF 194,800.–
Institut für molekulare Biologie, Universität Zürich, Zürich
Identification and characterization of novel genes involved in neoplastic growth and invasion

Beer Hans-Dietmar | KFS 02741-02-2011 | CHF 197,800.–
Dermatologische Klinik, UniversitätsSpital Zürich, Zürich
The function of the inflammasome protein TRIM16 in inflammation and cancer

Christofori Gerhard | KLS 02846-08-2011 | CHF 342,000.–
Institut für Biochemie und Genetik, Departement Biomedizin, Universität Basel, Basel
The molecular mechanisms underlying evasive resistance against anti-angiogenic cancer therapy

Detmar Michael | KFS 02821-08-2011 | CHF 350,900.–
Institut für pharmazeutische Wissenschaften, ETH Zürich, Zürich
Role of lymphatic cancer spread in organ metastasis

Hanahan Douglas | KFS 02868-08-2011 | CHF 246,100.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Targeting tumour metabolism with a copper chelator

Held Werner | KFS 02736-02-2011 | CHF 342,500.–
Centre Ludwig de l'Université de Lausanne pour la recherche sur le cancer, Université de Lausanne, Epalinges
NK cell mediated recognition of leukaemia

Hemmings Brian A. | KLS 02787-02-2011 | CHF 278,700.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Novel oncogenic mechanism of haematopoietic pathways in gliomagenesis

Hynes Nancy | KFS 02743-02-2011 | CHF 205,400.–
Friedrich Miescher Institut für biomedizinische Forschung (FMI), Basel
Role of the bone marrow niche in breast cancer metastasis and therapy response

Knuth Alexander | KLS 02740-02-2011 | CHF 53,200.–
Klinik und Poliklinik für Onkologie, UniversitätsSpital Zürich, Zürich
The mechanism underlying Coley's Fluid-mediated control of cancer

Lingner Joachim | KFS 02810-08-2011 | CHF 347,200.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Telomere instability and the DNA damage response in cancer: a proteomic approach

Müller Cristina | KLS 02762-02-2011 | CHF 324,100.–
Zentrum für radiopharmazeutische Wissenschaften, Paul Scherrer Institut (PSI), Villigen
Development and optimization of folate-based targeted radionuclide therapy of folate receptor-positive cancer diseases

Naegeli Hanspeter | KFS 02832-08-2011 | CHF 197,800.–
Institut für Pharmakologie und Toxikologie, Universität Zürich, Zürich
DNA repair of UV lesions in chromatin regulated by the chaperone-like ATPase p97 (Cdc48)

Nardelli Haefliger Denise | KFS 02808-08-2011 | CHF 200,400.–
Service d'urologie, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Immunotherapy of early uro-genital cancers in murine models and in non-muscle-invasive bladder cancer patients

Neri Dario | KFS 02839-08-2011 | CHF 196,500.–
Institut für pharmazeutische Wissenschaften, ETH Zürich, Zürich
Next-generation targeted cytotoxics for cancer therapy

Pabst Thomas | KFS 02733-02-2011 | CHF 232,100.–
Universitätsklinik für medizinische Onkologie, Inselspital, Universitätsspital Bern, Bern
A complex architecture of distal regulatory elements orchestrates the expression of myeloid key transcription factors; analysis of its deregulation in acute myeloid leukaemia (AML) patients

Petrova Tatiana | KFS 02863-08-2011 | CHF 233,800.–
Division d'oncologie expérimentale, Centre pluridisciplinaire d'oncologie (CePO), Centre hospitalier universitaire vaudois (CHUV) et Université de Lausanne, Epalinges
Transcriptional regulation of colon cancer metastasis

Plückthun Andreas | KFS 02841-08-2011 | CHF 239,200.–
Biochemisches Institut, Universität Zürich, Zürich
Tumour targeting of ErbB2 with designed ankyrin repeat proteins

Radtke Freddy | KFS 02807-08-2011 | CHF 350,200.–
Institut suisse de recherche expérimentale sur le cancer (ISREC), EPF de Lausanne, Lausanne
Uncovering and targeting the oncogenic properties of Notch in T-cell acute lymphoblastic leukaemia

Rüegg Curzio | KFS 02814-08-2011 | CHF 310,700.–
Département de médecine, Université de Fribourg, Fribourg
Unraveling cellular and molecular mechanisms of breast cancer metastasis to the brain

Santoro Raffaella | KFS 02732-02-2011 | CHF 197,800.–
Institut für Veterinärbiochemie und Molekularbiologie, Universität Zürich, Zürich
Role of TIP5 in epigenetic silencing process in cancer

Schäfer Beat W. | KLS 02784-02-2011 | CHF 217,500.–
Abteilung Onkologie, Kinderspital Zürich, Universitäts-Kinderkliniken, Zürich
Preclinical and mechanistic evaluation of FGFR4 signalling in rhabdomyosarcoma

Schoonjans Kristina | KFS 02809-08-2011 | CHF 312,000.–
Laboratory of integrative systems and physiology (LISP), Faculté des sciences de la vie, EPF de Lausanne, Lausanne
Exploration of the LRH-1-ASNS axis in liver tumourigenesis

Schwaller Jürg | KFS 02778-02-2011 | CHF 238,500.–
Departement Biomedizin, Universitätsspital Basel, Basel
Dissecting the cellular origin and molecular targets in MLL acute leukaemia

Stamenkovic Ivan | KFS 02766-02-2011 | CHF 320,600.–
Institut universitaire de pathologie de Lausanne (IUP), Centre hospitalier universitaire vaudois (CHUV), Lausanne
Analysis of the molecular mechanisms underlying the pathogenesis of Ewing's family tumours

Suter Beat | KFS 02748-02-2011 | CHF 349,800.–
Institut für Zellbiologie, Universität Bern, Bern
Proliferation and growth control activities of Drosophila Xpd/CAK

Walker Paul R. | KFS 02771-02-2011 | CHF 307,600.–
Centre d'oncologie, Hôpitaux universitaires de Genève (HUG), Genève
The impact of in vivo hypoxic microenvironments on anti-glioma immunity

Weber Achim | KLS 02773-02-2011 | CHF 348,100.–
Institut für klinische Pathologie, UniversitätsSpital Zürich, Zürich
Comprehensive characterization and classification of murine and human hepatocellular carcinoma (HCC) to identify appropriate models for targeted anti-liver cancer therapy

Werner Sabine | KFS 02822-08-2011 | CHF 309,100.–
Institut für molekulare Gesundheitswissenschaften, ETH Zürich, Zürich
Roles and mechanisms of action of the growth and differentiation factor activin in skin carcinogenesis

Approved bursaries in 2011

Total funds allocated: CHF 541,599.–

Bill Ruben Michael | MD-PhD 02804-07-2011 | CHF 180,533.–
Characterization of surrogate markers for monitoring tumour angiogenesis (MD-PhD bursary)
Destination: Labor Gerhard Christofori, Institut für Biochemie und Genetik, Universität Basel, Basel

Moor Andreas | MD-PhD 02806-07-2011 | CHF 180,533.–
Investigation of progesteron-induced signalling through RANKL, Wnt, and osteopontin in breast tumour progression using intraductal xenografting models (MD-PhD bursary)
Destination: Laboratoire Michel Aguet, Institut suisse de recherche sur le cancer (ISREC), EPF de Lausanne, Lausanne

Wampfler Julian Jan-David | MD-PhD 02805-07-2011 | CHF 180,533.–
Analysis of the HIC1/SIRT1 molecular pathway in acute myeloid leukaemia (MD-PhD bursary)
Destination: Labor Mario Tschan, Departement für klinische Forschung, Universität Bern, Bern

Presentation of approved research projects in 2011

Andres Anne-Catherine | **The molecular mechanisms provoking the ephrin-B2 induced deregulation of the mammary stem cell niche and leading to metastatic tumour growth** (KLS 02825-08-2011)
Duration: 01. 03. 2012 – 28. 02. 2013

Stem or progenitor cells represent the origin of malignant growth, and thus the therapeutic management of cancer also implies the understanding of the control of stem cell homeostasis. We showed that deregulated EphB4 and ephrin-B2 expression in the mammary epithelium affects the stem cell niche and thereby contributes to the development of aggressive and metastasizing tumours.

In continuation of this project, our present research aims to analyse whether the aberrant differentiation pathway is intrinsic to the stem cell population or is brought about by disturbed signalling from the cells constituting their niche. Moreover, we aim to identify the transmitters of Eph-ephrin signalling by expression profiling of specific mammary epithelial subpopulations.

With this approach we intend to identify signalling mechanisms ensuring stem cell homeostasis, which may lead to the elaboration of stem cell-targeted therapeutic interventions.

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Basler Konrad | **Identification and characterization of novel genes involved in neoplastic growth and invasion** (KFS 02749-02-2011)
Duration: 01. 10. 2011 – 01. 10. 2014

Cancer development is a complex process, the progression of which involves multiple genetic alterations. Research in recent decades has led to the discovery of many cancer genes. However, many more genes required for tumour growth remain to be unearthed.

Our aim is to identify such genes and to understand how they functionally connect to known cancer-related genes. We perform our studies in the model organism *Drosophila melanogaster.* By taking advantage of the excellent and extensive genetic toolkit that is available for *Drosophila,* we are able to generate tumours in the fly and to selectively remove single gene functions within these tumours. We then monitor the consequences of this loss on tumour growth.

This approach should allow us to identify genes that previously have not been known to play a role in cancer development. These findings can be translated into approaches that open avenues for therapeutic intervention in the treatment of different cancers.

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Beer Hans-Dietmar | **The function of the inflammasome protein TRIM16 in inflammation and cancer** (KFS 02741-02-2011)
Duration: 01. 10. 2011 – 01. 10. 2014

An inflammation represents the attempt of the immune system to restore tissue homeostasis after its disturbance by a stressor. Paradoxically, inflammation can also induce cancer development and supports tumour growth. Ultraviolet (UV) irradiation of the skin causes sunburn, which is mediated by the activation of a protein complex called inflammasome, expressed by keratinocytes. UV irradiation induces also skin cancer.

Therefore, the relationship between sunburn/inflammasome activation and cancer development will be examined. TRIM16 is a protein required for inflammasome activation in UV-irradiated keratinocytes. The function of this protein in the skin of mice during inflammation, sunburn, and carcinogenesis will be analysed.

This could result in the development of new strategies and drugs that suppress UV-induced carcinogenesis of the skin and inhibit tumour growth.

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Christofori Gerhard | **The molecular mechanisms underlying evasive resistance against anti-angiogenic cancer therapy** (KLS-02846-08-2011)
Duration: 01.03.2012 – 28.02.2015

Tumour outgrowth is dependent on the formation of new tumoural blood vessels (angiogenesis), and the inhibition of tumour neovascularisation provides a promising strategy for cancer treatment. The first anti-angiogenic therapies are now in routine clinical use. However, current clinical experience reveals that these anti-angiogenic therapies, although resulting in significant progression-free survival, only marginally extend overall survival. Apparently, tumours recur and overcome anti-angiogenic treatments by developing evasive or adaptive resistance.

In our project, we employ mouse models of cancer and gene expression profiling experiments to identify the molecular mechanisms underlying the development of evasive resistance to anti-angiogenic therapy. Once the critical molecular players are known, such observations need to be validated in cancer patients.

We hope that the identification of novel molecular targets will enable the design of improved anti-angiogenic cancer therapies.

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Detmar Michael | **Role of lymphatic cancer spread in organ metastasis** (KFS 02821-08-2011)
Duration: 01.03.2012 – 28.02.2015

In the majority of advanced human cancers, tumour cells first metastasize to lymph nodes. It is currently unclear and controversial whether lymph node metastases might actively promote the further spreading of tumour cells to other organs in the body.

The aim of our study is development of new experimental models for breast cancer and malignant melanoma of the skin to answer this question. We will permanently label tumour cells that have metastasized to the lymph nodes. If we can then detect labelled tumour cells also in organ metastases, this indicates that the lymph node metastases have indeed actively contributed to the further tumour spread. We will develop completely new labelling methods using heat-induced permanent fluorescent labelling and/or uptake of fluorescent nanoparticles.

The results of these studies will have an important influence on the understanding and therapy of human cancers.

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Hanahan Douglas | **Targeting tumour metabolism with a copper chelator** (KFS 02868-08-2011)
Duration: 01.01.2012 – 31.01.2013

In this study, we will examine the role of copper in tumour growth and metabolism. We hypothesize that copper chelation will result in decreased mitochondrial ATP production and increased accumulation of reactive oxygen species (ROS) via inhibition of two copper-dependent enzymes, cytochrome c oxidase and superoxide dismutase 1, respectively, thereby inhibiting cell proliferation while promoting a switch to aerobic glycolysis. We will test this hypothesis by measuring the activities of these enzymes and their products. We will also examine whether the ATP sensor AMPK is activated by copper limitation, and if so, whether it leads to increased dependence on glycolysis for ATP production and survival, by assessing a synergistic effect of glycolysis inhibition.

Our studies will establish a foundation for future clinical trials that combine copper chelation with glycolysis inhibitors, seeking to eradicate cancer cells that are addicted to glucose under insufficient bioavailable copper.

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Held Werner | **NK cell-mediated recognition of leukaemia** (KFS 02736-02-2011)
Duration: 01.09.2011 – 01.09.2014

New drugs are able to suppress specific types of leukaemia for prolonged periods of times, yet they often fail to cure leukaemia. If other treatment options fail, leukaemia patients may be treated using stem cell transplantation. Although this treatment option bears significant risks, it does have the potential to cure leukaemia. The reason for the cure is thought to be an immune response against residual leukaemic cells.

Using a combination of defined leukaemia models and stem cell transplantation, we aim to find out: (1) whether natural killer (NK) cells have the capacity to recognize and eliminate the cell of origin of leukaemia, the leukaemia stem cells, (2) whether the efficacy of NK cells depends on the specific type of leukaemia, and (3) whether the efficacy of NK cells can be improved.

These investigations are designed to determine whether NK cells can contribute towards curing specific types of leukaemia.

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Hemmings Brian A. | **Novel oncogenic mechanism of haematopoietic pathways in gliomagenesis**
(KLS 02787-02-2011)
Duration: 01. 08. 2011–01. 08. 2014

Glioblastoma multiforme (GBM) is the most common and deadly form of brain cancer. Despite intensive research, the median survival of GBM remains at one year, with less than 10% of patients surviving over five years. Our microarray analysis of GBM samples showed increased expression of SYK, mainly known in a haematopoietic context. Importantly, we verified that SYK was expressed in the GBM tissue, and overexpression seen on the microarray was not due to infiltrating lymphocytes.

We will now investigate molecular interactions of SYK in GBM cell lines. We will also study the tumour promoting role of SYK in GBM using normal untransformed astrocytes *in vitro* and *in vivo*. Due to our preliminary results, we will test the anti-tumour potential of SYK inhibitors *in vivo,* studying in particular the efficacy of therapeutics to cross the blood-brain barrier and the effect of inhibiting the immune system in tumour progression with the ultimate goal of discovering alternative treatments for GBM.

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Hynes Nancy | **Role of the bone marrow niche in breast cancer metastasis and therapy response**
(KFS 02743-02-2011)
Duration: 01. 09. 2011–01. 09. 2013

Breast cancer, although treatable at an early stage, is a significant clinical problem once progressed to metastatic disease. Latent metastasis leading to patient relapse occurs frequently in breast cancer, with the majority arising in the bone.

We propose that in the bone marrow the interaction between tumour cells and surrounding stromal cells form a protective niche that protects tumour cells from current therapies. Using *in vivo* models of breast cancer metastases, we will examine the gene expression of the bone stromal cells to identify changes that occur in response to tumour metastases. In parallel we will examine the changes that occur in breast carcinoma cells at the primary and metastatic sites.

These findings will identify pathways in tumour cells and the surrounding stroma that may be targeted to affect the survival of metastasis. Therapeutic targeting of tumour cells alone is currently not sufficient to eliminate bone metastasis. Through a better understanding of the cross-talk between breast carcinoma and the stromal microenvironment, this study will provide insights to help develop effective therapy for improved treatment and elimination of metastatic disease.

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Knuth Alexander | **The mechanism underlying Coley's Fluid-mediated control of cancer** (KLS 02740-02-2011)
Duration: 01. 07. 2011–01. 07. 2012

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 immunotherapy, although without knowing it. Coley observed that patients' tumours disappeared after an infection and began to systematically investigate this observation. He found that some patients injected with dead bacteria indeed showed tumour regression. Since then, our knowledge of the immune system has drastically increased. We think that Coley's Toxins activate the dendritic cells and thus results in better tumour-specific immunity and tumour control.

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; the second aims to investigate whether the controlled use of Coley's Toxins can be a therapeutic modality for cancer patients.

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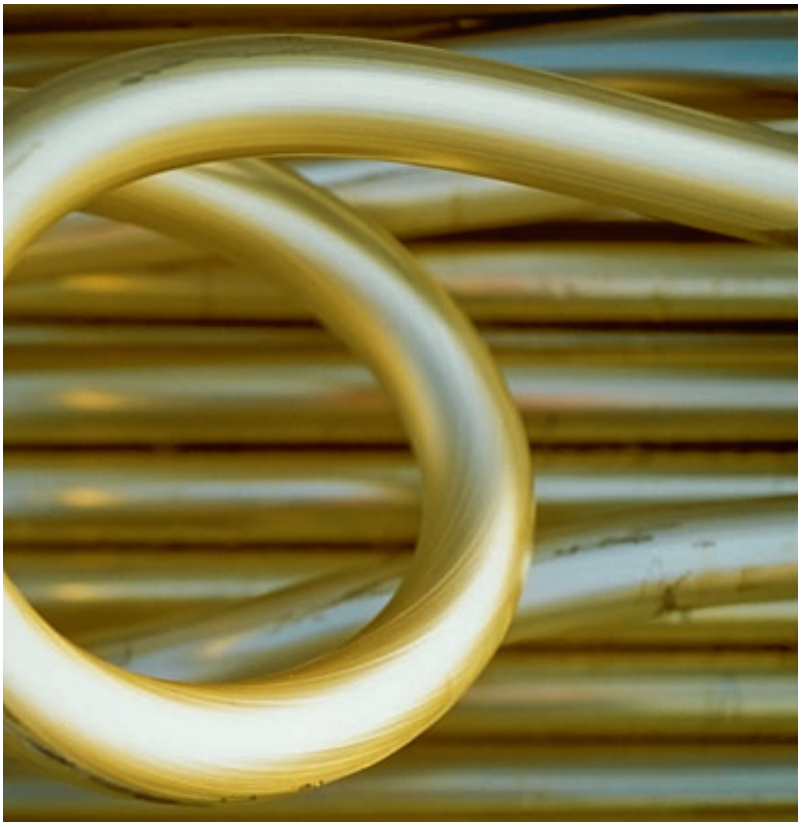

Lingner Joachim | **Telomere instability and the DNA damage response in cancer: a proteomic approach** (KFS 02810-08-2011)
Duration: 01. 04. 2012 – 31. 03. 2015

The ends of eukaryotic chromosomes, known as telomeres, function as cellular clocks. With the doubling of chromosomes, which precedes cell division, telomeres get shorter. When reaching a critical length, short telomeres are recognized by specialized factors that instruct the cells to stop dividing. Such cells are called senescent. Senescence occurs in order to suppress uncontrolled cell growth and formation of life-threatening tumours.

We have been developing novel technologies that allow us to elucidate the protein composition of telomeres. We will now investigate which structural changes occur at telomeres during senescence in order to suppress tumourigenesis.

Our results will contribute to the understanding of cancer formation. In addition, elucidation of the molecular structure of senescence-inducing telomeres may facilitate the early detection of precancerous lesions in patients and allow testing of the effects of novel telomere-targeting cancer therapies.

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Müller Cristina | **Development and optimization of folate-based targeted radionuclide therapy of folate receptor-positive cancer diseases** (KLS 02762-02-2011)
Duration: 01. 10. 2011 – 01. 10. 2014

Folic acid has emerged as a promising targeting ligand for selective delivery of attached probes to folate receptor (FR)-positive cancer cells. Radiofolates are well established for imaging but not for therapeutic purposes. Therefore, the topic of this project will be to evaluate and investigate folate conjugates of particle-emitting radioisotopes *in vitro* and *in vivo*.

Folate conjugates modified with an albumin-binding entity and labelled with various therapeutic radioisotopes (alpha and beta-emitters) will be tested and selected for FR-targeted radionuclide therapy. Furthermore, radionuclide therapy will be investigated in combination with chemotherapeutics (e.g., Pemetrexed) and radiosensitizing agents. Radionuclide therapy with somatostatin analogues is successfully employed to reduce tumour progression and to improve quality of life of patients with neuroendocrine cancer. Of about 17,500 people that are diagnosed with common cancer diseases each year in Switzerland, about 56% suffer from FR-positive tumours. Hence, implementation of FR-targeted radionuclide tumour therapy would be of clinical interest, because it may improve quality of life of a large number of patients.

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Naegeli Hanspeter | **DNA repair of UV lesions in chromatin regulated by the chaperone-like ATPase p97 (Cdc48)** (KFS 02832-08-2011)
Duration: 01.04.2012 – 31.03.2015

The frequency of sunlight-induced skin cancer has been increasing dramatically. The ultraviolet (UV) radiation of sunlight generates damages to the genome that, in the absence of repair, lead to skin cancer. However, the genome is packed in the form of an approximately two meter-long filament within the cell nucleus, which has the dimensions of a few hundredths of a millimeter. The question is, therefore, how UV damage can be located and repaired despite such a high level of compaction.

We have discovered a new regulatory system that coordinates the spatial and temporal sequence of events during DNA repair. The key regulator is a protein known as p97. Next, we plan to investigate how exactly p97 regulates the DNA repair of UV lesions, and which additional accessory factors are involved.

Knowledge of this regulatory system provides a basis for precautionary measures to reduce skin cancer rates. Also, p97 is a potential target for new anti-cancer therapeutic strategies.

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Nardelli Haefliger Denise | **Immunotherapy of early uro-genital cancers in murine models and in non-muscle-invasive bladder cancer patients**
(KFS 02808-08-2011)
Duration: 01.02.2012 – 31.01.2015

Vaccination to induce anti-tumoural responses is a promising strategy for treating cancer, although limited clinical results have been obtained to date. We recently demonstrated that an intravaginal immunostimulation in addition to vaccination greatly improved regression of genital tumours in an animal model of cervical cancer. Indeed, intravaginal application of diverse molecular or bacterial agents increased the number of anti-tumoural CD8 T-cells induced by vaccination. Similar results were obtained when we administered such agents in the bladder, though differences (type of immunostimulant and efficient vaccination routes) were noticed.

In this project, we will determine the mechanisms underlying intravaginal immunostimulation and potential differences with intravesical instillation, aiming toward optimization or personalization of this treatment to the localization of the tumour.

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Neri Dario | **Next-generation targeted cytotoxics for cancer therapy** (KFS 02839-08-2011)
Duration: 01.01.2012 – 31.12.2014

Cancer chemotherapy relies on the administration of drugs that often damage not only tumour cells but also normal cells in rapid proliferation (e.g., mucosae, bone marrow, hair follicle, intestinal epithelium). These toxic pharmaceutical agents typically do not preferentially localize at the tumour site (where their action would be needed), thus causing undesired toxicities to normal organs and preventing dose escalation to regimens that would be necessary to induce cures. For this reason, it is desirable to develop cancer therapies that deliver cytotoxic drugs to malignant cells while sparing normal tissue.

At present, monoclonal antibodies (i.e., large proteins that are part of our immune system) are being considered as "vehicles" for the selective delivery of chemotherapeutic agents to the tumour site. This research activity led in 2011 to the approval of brentuximab vedotin, an antibody-drug conjugate used for the treatment of Hodgkin's lymphoma. However, recent studies indicate that small organic molecules with high affinity to targets present in large amount in the tumour ("tumour-associated antigens") may be even better than antibodies as pharmacodelivery vehicles, thanks to their ability to diffuse rapidly into the tumour mass and to clear out of the body.

In this project, we will use innovative chemical methodologies for the isolation of highly selective ligands to carbonic anhydrase IX (CAIX) and to prostate-specific membrane antigen (PSMA), two proteins that are present in large amounts in certain cancer types but that are otherwise present only at low levels in normal tissues. The new small organic ligands will be coupled to chemotherapeutic agents, and the resulting conjugates will be tested for their ability to improve cancer chemotherapy.

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Pabst Thomas | **A complex architecture of distal regulatory elements orchestrates the expression of myeloid key transcription factors; analysis of its deregulation in acute myeloid leukaemia (AML) patients**
(KFS 02733-02-2011)
Duration: 01. 07. 2011 – 01. 07. 2013

This study will investigate how the expression of important transcription factors regulates the pathogenesis of acute myeloid leukaemia through both close and distant regulatory elements. This will help us better understand how important transcription factors can be misregulated in patients with acute myeloid leukaemia. We are hoping that the improved understanding of the misregulation of important transcription factors will improve therapeutic approaches.

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Petrova Tatiana | **Transcriptional regulation of colon cancer metastasis** (KFS 02863-08-2011)
Duration: 02. 01. 2012 – 01. 01. 2015

Tumour metastasis is a leading cause of cancer-related mortality, but the mechanisms regulating the growth of metastatic lesions are not well understood. Transcription factor Prox1 is an important regulator of organogenesis during development, where it controls cell fate decisions and cell differentiation. We previously showed that Prox1 is overexpressed in colorectal cancer, where it is important for the transition from adenoma to carcinoma *in situ*. More recently, we found that in advanced carcinomas, Prox1 promotes development of macrometastases.

In this project, we will study how Prox1 promotes macrometastasis formation and identify the regulators of Prox1 activity in colon cancer cells.

The outcome of these studies may be directly relevant for the development of better treatment strategies for metastatic colorectal cancer.

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Plückthun Andreas | **Tumour targeting of ErbB2 with designed ankyrin repeat proteins** (KFS 02841-08-2011)
Duration: 01. 01. 2012 – 31. 12. 2013

Depositing therapeutic payloads specifically on the site of tumour represents a major challenge in current tumour therapy approaches. We have developed a new class of binding molecules called "designed ankyrin repeat proteins" (DARPins). Due to their favourable properties, these binders are expected to improve significantly the efficacy of tumour targeting. It has even become possible to construct vehicles capable of inducing programmed cell death (apoptosis) of breast tumour cells in the absence of therapeutic payloads or other tumouricidal additives. Hence, the adverse side effects associated with conventional tumour therapy could be eliminated.

In the ongoing study, we will further examine the molecular mechanisms of the anti-tumour action of DARPins as well as the efficacy of DARPin treatment *in vivo*. Such investigations will facilitate the development of novel therapeutic substances with improved efficacy and grossly reduced side effects.

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Radtke Freddy | **Uncovering and targeting the oncogenic properties of Notch in T-cell acute lymphoblastic leukaemia** (KFS 02807-08-2011)
Duration: 01. 01. 2012 – 31. 12. 2014

T-cell acute lymphoblastic leukaemia (T-ALL) is caused by aberrant growth of thymic progenitor cells. Over 50 % of human T-ALLs (throughout all the different subclasses) exhibit mutations within the Notch1 gene, leading to the continuous activation of the Notch cascade. Notch1 activation results in the expression of various target genes, including Hes1. Hes1 is the best-known Notch target gene, which functions as transcriptional repressor. Our studies

showed that Hes1 is critical for the development and maintenance of murine and human T-cell leukaemia. Reducing Hes1 levels in leukaemic cells induces cell death of the tumour cells.

This study aims at addressing two important questions: (1) which Hes1-regulated target genes confer oncogenic properties in Notch-induced T-ALL, and how?, and (2) can we identify new inhibitors that target the oncogenic properties of Notch1 without causing major side effects?

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Rüegg Curzio | **Unraveling cellular and molecular mechanisms of breast cancer metastasis to the brain** (KFS 02814-08-2011)
Duration: 01.03.2012 – 28.02.2015

Early breast cancers can be effectively cured in 80–90% of the cases, whereas advanced or metastatic cancers have a poor prognosis. Over one-quarter of patients develop brain metastasis, and this frequency is increasing. There is thus an urgent need to develop more effective therapies.

Goals
We will elucidate mechanisms of metastasis, in particular cellular and molecular events promoting the seeding, colonization, and outgrowth of disseminated cancer cells. Questions addressed are: (1) how breast cancer cells enter into the brain, (2) how they interact with brain cells, and (3) what the role of the immune system is in controlling brain metastasis.

Methods
We will use a model of breast cancer metastasis to the brain developed in our lab to address the research questions. Patient-derived material will be used to validate experimental results.

Results
We have already identified many genes expressed in brain metastatic cancer cells. Inhibition of some of these genes leads to reduced brain metastasis formation. We are currently investigating the functional role of selected molecules in the metastatic process.

Benefits for the patients
We expect to identify novel therapeutic targets to prevent and treat brain metastases of breast cancer. We have already identified one target against which there is a drug in clinical development.

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Santoro Raffaella | **Role of TIP5 in epigenetic silencing process in cancer** (KFS 02732-02-2011)
Duration: 01.11.2011 – 01.11.2014

Aberrant epigenetic modifications play major roles in cancer. The reversible nature of epigenetics is an important opportunity to establish therapeutic strategies aimed at reversing transcriptional abnormalities in tumours. For these clinical applications, the mechanistic insights initiating epigenetic alterations in cancer must be elucidated. TIP5 recruits enzymes that epigenetically modify and repress transcription of rRNA genes. Our preliminary data showed upregulation of TIP5 in tumours and involvement of TIP5 in repressing transcription of tumour suppressor genes in metastatic prostate cancer.

Through an integrative transcriptomic and epigenomic approach and *in vivo* functional analysis, the role of TIP5 in metastasis will be investigated. Our aim is to determine the mechanisms establishing aberrant epigenetic modifications at tumour suppressor genes that are implicated in metastasis and to develop novel strategies allowing the reversal of gene silencing for cancer prevention and therapy.

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Schäfer Beat W. | **Preclinical and mechanistic evaluation of FGFR4 signalling in rhabdomyosarcoma** (KLS 02784-02-2011)
Duration: 01.01.2012 – 01.01.2014

Aberrantly activated proteins are fundamental for cancer development and therefore represent targets for therapy. FGFRs have been found to be activated by mutation in different tumours including FGFR4 in the paediatric tumour rhabdomyosarcoma (RMS). Our preliminary data showed that FGFR4 might be an important factor influencing the efficacy of current and experimental RMS therapies.

We therefore plan to characterize the benefit RMS cells have from high FGFR4 activity on the molecular level, especially under treatment conditions, and we plan to test whether the protein could serve as single target for therapy or whether targeting could improve therapeutic effect

in combination with established therapies. For this approach, we plan to use both cell line and *in vivo* xenograft models of RMS.

Characterization of FGFRs as regulator of therapy response might lead to a better understanding of resistance to therapy and might help to improve therapy success in general in tumours with deregulated FGFR pathways.

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Schoonjans Kristina | **Exploration of the LRH-1-ASNS axis in liver tumourigenesis** (KFS 02809-08-2011)
Duration: 01. 02. 2012 – 31. 01. 2015

Cancer cells require large amounts of nutrients, including amino acids, to achieve rapid cell division and growth. Evidence is now emerging that the enzyme asparagine synthetase (ASNS), which is important for the production of the amino acid asparagine, may be crucial for tumour survival. Recently, we identified that the nuclear receptor, LRH-1, is indispensable to adequately control the expression of ASNS in the liver.

In this project, we plan to study ASNS regulation by the nuclear receptor LRH-1 and to establish its impact on liver carcinogenesis by an as-yet-unknown regulatory mechanism. We will use a combination of genetic and pharmacological approaches to establish the pro-tumourigenic potential of LRH-1 in the liver.

The outcome of this study should lead to new insights on how amino acids in general and asparagine in particular ultimately converge with pathways that control tumour survival. Following upon the established pro-tumourigenic function of LRH-1 and ASNS in other cells or organs, we expect that our results will lead to new therapeutic strategies to treat liver cancer.

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Schwaller Jürg | **Dissecting the cellular origin and molecular targets in MLL acute leukaemia** (KFS 02778-02-2011)
Duration: 01. 07. 2011–01. 07. 2013

Mixed lineage leukaemia (MLL) fusions are recurrently found in acute leukaemia with a poor prognosis. MLL fusions induce leukaemia through aberrant transcription mediated by a dynamically assembled protein complex. We established conditional transgenic MLL leukaemia mice to explore the impact of the cellular origin, to characterize critical protein interactions of the MLL complex, and to search for novel therapeutic targets. Activation of an MLL fusion in haematopoietic stem cells resulted in an aggressive disease with a particular genetic signature. Structure function analysis dissected critical molecular interactions within the MLL complex. A high throughput knockdown screen revealed candidate protein kinases regulating growth and differentiation of leukaemic cells.

We are currently validating these observations, which will provide important insights for the development of novel therapeutic strategies for MLL acute leukaemia.

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Stamenkovic Ivan | **Analysis of the molecular mechanisms underlying the pathogenesis of Ewing's family tumours** (KFS 02766-02-2011)
Duration: 01. 11. 2011–01. 11. 2014

Ewing sarcoma family tumours (ESFT) are highly aggressive malignancies of the bone and soft tissues that occur primarily in children and young adults. They are the second most frequent cancer of the bone in children and bear a very poor prognosis once they have disseminated, despite multimodal therapy. ESFT are characterized by a unique chromosomal translocation that gives rise to a fusion gene composed of EWS and a transcription factor of the Ets family known as FLI1. The EWS-FLI1 protein acts as an aberrant transcription factor that can both induce and repress numerous genes, whose altered expression is believed to lead to tumour formation. Recently, we discovered a subset of cells in ESFT known as cancer stem cells (CSC) that constitute its driving force and that are responsible for relapse following treatment.

We are now characterizing these cells and will address the mechanisms that govern their emergence. It is believed that therapeutic targeting of CSCs is going to be crucial in curing a variety of cancers, such that understanding their biological properties will be required if they are to be eliminated. We are pursuing the study of epigenetic mechanisms that underlie ESFT CSC emergence with the goal of identifying such mechanisms and subjecting them to novel therapeutic approaches.

The benefit to patients will be the development of a rational mechanism-based therapy that should substantially improve the prognosis of one of the most aggressive paediatric tumours.

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Suter Beat | **Proliferation and growth control activities of Drosophila Xpd/CAK** (KFS 02748-02-2011)
Duration: 01. 08. 2011–01. 08. 2014

The availability of a large variety of sophisticated genetic tools made invertebrate model systems prime choices for the exploration of cellular control processes. They are thus well suited to study the cellular mechanisms in place to prevent cancer formation. Human patients with defects in XPD display different syndromes, and some of them are associated with a 1000-fold increase in cancer risk. We showed that *Drosophila* XPD controls several physiological processes, and problems with any of these functions can lead to the development of cancer. XPD sits at the intersection between different important cellular control processes, and in this position it controls and dispatches a potent activator of growth, proliferation, and cell division.

We will explore the molecular genetic basis of this control mechanism. Because these basic control mechanisms have been conserved during evolution, we expect our findings to be relevant not only for XPD patients but also more generally for cancer patients.

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Walker Paul R. | **The impact of *in vivo* hypoxic microenvironments on anti-glioma immunity**
(KFS 02771-02-2011)
Duration: 01.10. 2011–01.10. 2014

Immunotherapy for malignant brain tumours such as glioblastoma has great potential, but clinical efficacy may be compromised by the hypoxic tumour microenvironment. Tumour cells adapt to low oxygen by expressing hypoxia-inducible factor 1 (HIF-1), which enhances their survival. Hypoxia also impacts on immune cells, but the consequences are only partly defined.

In this study, we will explore the critical issue of immune cell-tumour cell interactions when both cell types are subjected to low oxygen tensions. Cellular interactions will be studied *in vitro* either under conventional conditions or in a hypoxic chamber, and *in vivo* in mouse tumour models. We will also modulate HIF-1 using novel drugs.

The expected results of the project will guide development of immunotherapies for patients with brain tumours that can function optimally in association with other treatment modalities in a hypoxic microenvironment at the tumour site in the brain.

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Weber Achim | **Comprehensive characterization and classification of murine and human hepatocellular carcinoma (HCC) to identify appropriate models for targeted anti-liver cancer therapy**
(KLS 02773-02-2011)
Duration: 01. 01. 2012 – 01. 01. 2015

Liver cell tumours of different mouse models of liver tumour development are characterized at the morphological and molecular levels. It is the aim of this study to develop a classification of murine tumours based on these findings and to test the applicability of this classification to human liver cell tumours. To this purpose, murine tumours will be analysed at the microscopic, immune phenotypic, and genetic levels, i.e., mutational and gene expression analyses. Based on these results, tumours will be grouped and subtypes defined. This is followed by analysis of human liver cell tumours concerning the question as to what subtypes of murine tumours most closely reflect what groups of human tumours.

These studies potentially lead to the identification of murine models reflecting certain subtypes of human liver cell tumours, which is a prerequisite for testing targeted molecular therapies.

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Werner Sabine | **Roles and mechanisms of action of the growth and differentiation factor activin in skin carcinogenesis** (KFS 02822-08-2011)
Duration: 01. 02. 2012 – 31. 01. 2015

The number of patients suffering from basal or squamous cell carcinoma of the skin is continuously increasing. Therefore, it is important to identify the mechanisms underlying the development and malignant progression of skin cancer. In our project funded by the Cancer Research Switzerland foundation, we identified the growth and differentiation factor activin as a potent tumour-promoting molecule in the skin. Activin affects different components of the immune system, resulting in a tumour-promoting microenvironment.

We will now determine the mechanisms of activin action in skin carcinogenesis, with particular emphasis on the effect of activin on T-lymphocytes. In addition, we will determine if inhibition of activin action reduces skin carcinogenesis and malignant progression of skin tumours in mice.

This would be a prerequisite for a possible use of activin antagonists in patients with skin cancer.

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Oncology nursing research

The aim of cancer research is to decrease cancer incidence and mortality but also cancer-caused morbidity, the incidence of disease within a population. Cancer research comprises studies in basic research, translational research, clinical research, health services research, and outcome research. End points are mortality rate, quality of life, or cost-benefit analyses, for example. In Switzerland, mainly national and international studies in basic and clinical research are conducted successfully, although in recent years there has been a drop in clinical research [1]. For this reason the National Cancer Programme 2011–2015 (NCP) promotes translational and clinical research in particular. Precisely in these areas, oncology nursing research can make a valuable contribution, because in translation research the object is to test the findings of basic research in real treatment settings [1, 2]. Nursing research topics include, for instance, symptoms that accompany disease or supporting self-management in patients and their families.

National and international research priorities

The objectives of cancer research follow international priorities. The United States (US) National Cancer Institute conducts and supports clinical and translational research in the framework of coordinated, broad-based, and interdisciplinary programmes [2]. Translational research is also a research focus of the Oncology Nursing Society [3]. Correspondingly, the US National Institute of Nursing Research, the European Oncology Nursing Society, *Onkologiepflege Schweiz,* and the *Akademische Fachgesellschaft Onkologiepflege* of the Swiss Association for Nursing Science (ANS) focus on the following research topics: health promotion and prevention, reducing health disparities, nursing care, and symptom management and self-management [3, 4, 5, 6, 7].

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A recent systematic review of the literature examined the current contribution of oncology nursing in Switzerland. The review looked at publications in oncology nursing in the years 2005–2009 in the following databases: PubMed, Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane Reviews, and the Joanna Briggs Institute (JBI) database at the University of Adelaide, South Australia. A total of 143 articles were analysed in detail. The literature review showed that 70 % of the publications were descriptive and observational studies [8]. Nursing science is also publishing more findings on the effectiveness of nursing interventions. To illustrate some current focuses of oncology nursing research in Switzerland, three research studies are presented in the following. The research builds especially on experience and findings from the US and the UK.

Promotion of pain self-management

An example of this knowledge transfer is the PRO-Self© Plus Pain Control Program, a self-care intervention to improve cancer pain management that was developed in the US [9]. The programme was translated into German in close collaboration with the US research team and tested in a pilot study at the Tumorzentrum Ludwig Heilmeyer – Comprehensive Cancer Center at the University Medical Center in Freiburg, Germany. Initial results showed that the intervention significantly increased patients' knowledge about pain management, but pain reduction remained moderate. Based on these results, the programme is being adapted with the goal of increasing the pain reduction. At the present time, a multicentre, randomized, controlled study is being planned for Switzerland. In the study, which will be conducted at several centres simultaneously, patients will be randomly assigned to different study groups. A comparison of patients with the pain control programme with patients without this intervention will allow conclusions to be drawn about the success of the pain control programme. If the programme is found to be effective in this large study, nurses could use this intervention in future in Switzerland to support pain self-management by patients with cancer [10].

Self-assessment of postoperative symptoms

A PhD project at the University of Basel dealt with tumours of the external female genitalia (vulval intraepithelial neoplasia and vulvar carcinoma), a group of little researched and rare cancers. Despite frequent postoperative complications with these patients, there exists no instrument for self-assessment of symptoms after surgery. A team of nursing science and medical researchers from Switzerland, Germany, and the US developed and validated an assessment instrument as a way for women with vulval neoplasia to describe their symptom experience. In a cross-sectional study at university clinics in Berlin, Düsseldorf, Freiburg, Munich, Basel, Bern, and Zurich and at St. Gallen Cantonal Hospital the measurable psychological characteristics of the newly developed assessment instrument for the patients and the frequency of the symptoms described are currently being examined. The aim is to implement this kind of self-assessment to promote early recognition and treatment of symptoms in research and clinic [11]. The study is at the same time a contribution to the research focus "reduce health disparities", as rare forms of cancer are being studied that have received little attention in research up to now [12]. The ultimate aim of the project is to significantly improve the care of patients with these cancers.

Symptom experience and self-management after stem cell transplantation

A third and ongoing nursing research study is examining self-management and symptom experience after stem cell transplantation. It is known that with haematopoietic stem cell transplantation (HSCT) there is a life-long increased likelihood of long-term physical and mental health problems. For early recognition of these problems, in addition to objective diagnoses especially patients' self-assessment of their symptoms is important. This multicentre study in Basel and Zurich is conducting an extensive survey of patients and developing an assessment instrument that measures symptom experience after HSCT. The study is using qualitative and quantitative research methods, and in content it is based on a database with symptom descriptions (PRO-CTCAE item bank) recently developed by the US National Cancer Institute. In the long term, the results of the study will be used to optimize after-care of patients after stem cell transplantation [13].

These three examples illustrate the interdisciplinary character of nursing studies. Depending on the nursing science topic, quantitative or qualitative research methods or a combination of both are used. Essential is the use of sound research methods, so that the effectiveness and the cost effectiveness of nursing interventions can be demonstrated [14]. The international connections in the research projects described above also help to strengthen Switzerland's networking as a research centre [15].

Outlook and vision

In the future, nursing research in Switzerland should invest more in the development, implementation, and testing of the effectiveness of new care models in which, for example, also new professional roles such as Advanced Practice Nurses (APNs) are integrated. APNs are registered nurses who have gained advanced training for expanded clinical practice by earning a Master's degree in nursing; they work primarily clinically with patients and families. A systematic review of the literature in the US showed that acutely ill patients that were cared for by APNs had shorter hospital stays, with lower costs for their care [16]. A randomized controlled study found further that patients who were cared for by APNs and who received a palliative psychoeducation intervention for four weeks and monthly follow-ups up to the end of life had improved quality of life and less depression [17].

To realize oncology nursing research studies, nursing researchers obtain specialist and financial support from various institutions, such as the Swiss National Science Foundation, the Cancer Research Switzerland foundation, the cantonal cancer leagues, foundations and associations, and the pharmaceutical industry. The institutional framework for conducting research projects is offered by, among others, the institutes of nursing science at the University of Basel and the University of Lausanne and by universities of applied sciences that work together closely with clinical facilities and other disciplines. The central aim is to decisively improve the care of patients with cancer in Switzerland.

The research priorities set by national and international organizations in cancer research generally and in oncology nursing research in particular offer potential for development in Switzerland. Translational research in particular is a promising approach for study of the effectiveness and cost effectiveness of new care models in clinical practice [18]. To strengthen clinical and translational research it is important to further expand the research and training infrastructure at the universities and universities of applied sciences. Up to now, research institutions worked together mainly with hospitals; in the future, collaborations should also be developed with other institutions in the health care system, such as outpatient facilities and nursing homes. Through networking the various research disciplines and research settings and conducting more intervention studies, nursing science researchers could make a significant contribution towards raising the quality of cancer research in Switzerland – and thus to patient benefit.

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After completing her education and training in general nursing, Beate Senn worked first at Hüttenhospital Dortmund in Germany and at Zieglerspital in Bern in the gerontology and surgery wards. From 2001 to 2007 she taught at the education centre of the Inselspital in Bern in the areas of health promotion, gerontology, care management, and gynaecology. She earned certifications in the field of education. While working as a vocational school teacher at the Berner Bildungszentrum Pflege (higher vocational school of nursing), she completed a Master's degree in nursing science at the Institute of Nursing Science, University of Basel. Since 2009 Senn has been conducting research both in Basel and at the Gynaecology Clinic at Bern University Hospital, focusing on symptom management in patients with vulvar neoplasms. Senn completed a doctorate in 2012.

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List of completed research projects in 2011

Bertoni Francesco | OCS 02296-08-2008 | CHF 126,500.–
Laboratorio di oncologia sperimentale, Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Genomic alterations and immunogenetics of Richter's syndrome, a diffuse large B-cell lymphoma subtype with very poor prognosis

Bertoni Francesco | KLS 02403-02-2009 | CHF 150,000.–
Laboratorio di oncologia sperimentale, Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Anaplastic large cell lymphoma: one or more entities?

Bron Luc | OCS 02191-02-2008 | CHF 333,100.–
Service d'ORL et de chirurgie cervico-faciale, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Identifying targets for, as well as overcoming barriers to, specific immunotherapy in human head and neck squamous cell carcinoma

Bubendorf Lukas | OCS 02285-08-2008 | CHF 227,100.–
Institut für Pathologie, Universitätsspital Basel, Basel
Detection and isolation of novel gene fusions in carcinomas by high-resolution genomic profiling

Cathomas Gieri | KLS 02392-02-2009 | CHF 248,550.–
Institut für Pathologie, Kantonsspital Baselland, Liestal
The role of polyomavirus in the development of Merkel cell and epithelial skin carcinomas

Chappuis Pierre Olivier | OCS 02073-04-2007 | CHF 305,800.–
Service d'oncologie, Service de médecine génétique, Hôpitaux universitaires de Genève (HUG), Genève
Prospective screening for hereditary nonpolyposis colorectal cancer (HNPCC) syndrome in a population-based setting

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 SAKK38/07 study)

Forrer Flavio | OCS 02259-08-2008 | CHF 107,000.–
Klinik und Institut für Radiologie und Nuklearmedizin, Kantonsspital Baselland, Bruderholz
Glucagon-like peptide 1 (GLP-1) receptor targeting a novel method for cancer imaging: design, synthesis, preclinical and clinical evaluation of radiolabelled GLP-1 chelator conjugates

Frattini Milo | OCS 02301-08-2008 | CHF 195,000.–
Laboratorio di diagnostica molecolare, Istituto cantonale di patologia (ICP), Locarno
Identification and characterization of predictive molecular markers in colorectal cancer patients treated with EGFR-targeted therapies

Körner Meike | OCS 02349-02-2009 | CHF 108,500.–
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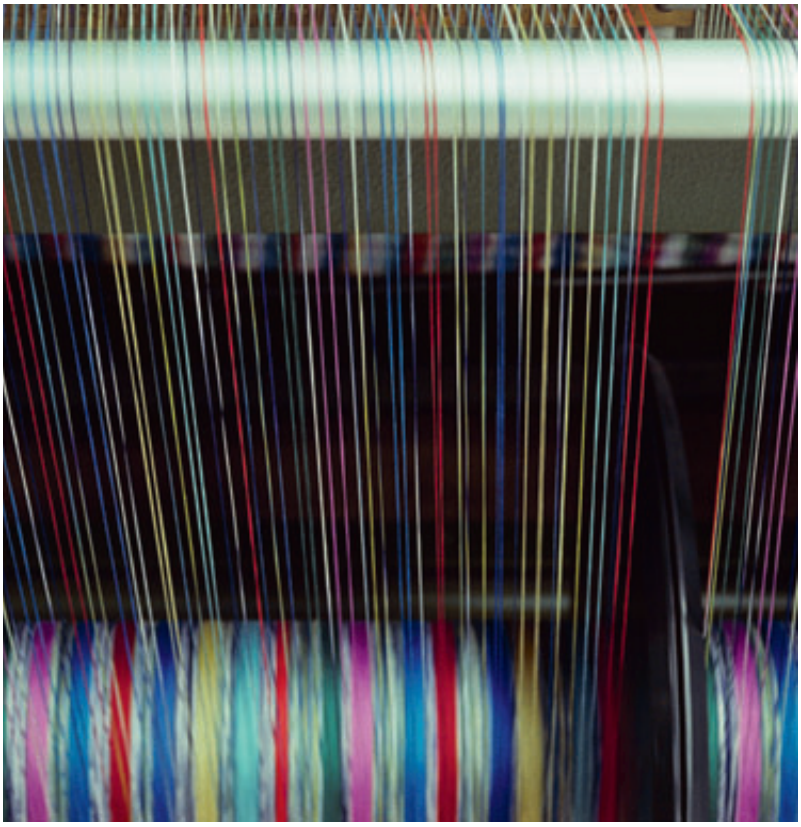
In vitro evaluation of the glucagon-like peptide 2 receptor expression in human cancer: molecular basis for in vivo tumour radiotargeting

Kristiansen Glen | KFS 02465-08-2009 | CHF 171,200.–
Institut für Pathologie, Universitätsklinikum Bonn (UKB), Bonn, Deutschland
Identification of a clinically applicable prognostic RNA signature of prostate cancer

Mamot Christoph | OCS 02270-08-2008 | CHF 247,900.–
Medizinische Onkologie, Kantonsspital Aarau, Aarau
Prospective evaluation of the predictive value of PET in patients with diffuse large B-cell lymphoma under R-CHOP-14, a multicentre study



Schwaller Jürg | OCS 02357-02-2009 | CHF 232,000.–
Departement Biomedizin, Universitätsspital Basel, Basel
Exploring new molecular therapeutic targets in MLL-X acute leukaemia

Speiser Daniel E. | OCS 02279-08-2008 | CHF 206,500.–
Clinical Tumor Biology & Immunotherapy Unit, Centre Ludwig de recherche sur le cancer,
Hôpital Orthopédique/CHUV, Lausanne
Immunotherapy of melanoma patients and analysis of the regulation of tumour antigen-specific CD4 and CD8 T-cells

Presentation of completed research projects in 2011

Bertoni Francesco | **Genomic alterations and immunogenetics of Richter's syndrome, a diffuse large B-cell lymphoma subtype with very poor prognosis** (OCS 02296-08-2008)

Richter's syndrome (RS) represents the development of a diffuse large B-cell lymphoma (DLBCL) in the context of chronic lymphocytic leukaemia (CLL). The pathogenesis of RS is still largely unknown. Analysis of RS has been often focused on the study of lesions previously identified in *de novo* DLBCL. However, we have previously shown that RS lacks many of the typical genetic lesions shown in DLBCL (Rossi et al., *Blood* 2011). Here, we applied an unbiased, genome-wide approach, searching for DNA copy number alterations in a large series of RS, comparing them with *de novo* DLBCL, CLL-phase of RS and untransformed CLL.

Material and methods

The study included 50 RS, 30 CLL-phases preceding RS, 130 DLBCL, 318 CLL. All RS were classified as DLBCL. DNA was extracted from frozen biopsies and was processed using the Affymetrix GeneChip Human Mapping SNP6 arrays. Differences in frequencies between subgroups were evaluated using Fisher's exact test. Clinical data were available in half of the cases, and genomic lesions were evaluated for their impact on clinical outcome with the log-rank test.

Results

In RS, the most common gains were +12 (40%), +4q12 (14%), +2p25.3–25.2 (13%), +8q23.3–qter (12%), +1q32.1, +2p16.1–13.2 (*BCL11A/REL*), +15q22.31–26.3, +18q21.33 (BCL2) (10%), and +3q24.1–q26.3 (9%). Amplifications were observed at the BCL2 locus and at 1q32.1. The most common losses were at 17p13.1 (*TP53;* 29%), 8p21.3 (*TNFRSF10A/B;* 15%), 8p23.3 (16%), 11q22.3 (*ATM*) (15%), 14q23.3 (13%), 7q33–35 (11%), 14q32.11 (10%), 14q32.31–32.33 (*TRAF3*), and 9p21.3 (*CDKN2A*) (9%). The latter locus was also the target of recurrent homozygous deletions.

RS appeared intermediate between CLL-phase and *de novo* DLBCL in terms of number of recurrent lesions. When compared with *de novo* DLBCL, RS presented less –6q23 (*TNFAIP3;*), –15q15.1–q21.1 (*B2M*), +7/7q, –6q21 (*PRDM1*), +2p16.1 (*BCL11A*), –1p36 (*TNFRSF14*), copy-neutral LOH at 6p25.3–21.32, +5p, +11q14.1–q25, +1q22–q41, +6p21. Conversely, RS presented more often +4q12, –7q33–35, –11q22.3 (*ATM*), –14q23.3. No statistical differences were observed for lesions such as +3/+3q, +8q, –8p, –9p21.3 (*CDKN2A*), +12q, +15q, –17p (*TP53*). Compared to CLL-phase, RS had significantly more gains at 1q32.1, 11q23.3, 11q24 and 9p21.3 losses (*CDKN2A*). The latter, as well as 18q gains and 8p losses, were also associated with a poorer overall survival in RS patients.

Compared to the large series of CLL with no history of transformation, CLL-phase samples presented less frequently losses at 13q14.3 (DLEU2, MIR15A, MIR16-1a), more commonly gains at 12, 4q12, +2p, and loss at TP53 locus.

Conclusions

DNA copy number changes in RS are intermediate between *de novo* DLBCL and CLL-phase. Recurrent lesions were identified that appeared to be more common in RS than in DLBCL and that seem to be involved in the progression from CLL to an aggressive lymphoma. Also, the acquisition of mono- and bi-allelic losses of CDKN2A appears to be one of the most important events in the transition from CLL-phase to RS. Additional studies are still ongoing, and data will be presented in the future.

The results so far obtained might allow the identification of patients with CLL carrying a higher risk of transformation to RS. Also, the identification of lesions affecting the cell cycle as the most common alteration might help in tailoring the treatment for RS patients.

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Bertoni Francesco | **Anaplastic large cell lymphoma: one or more entities?** (KLS 02403-02-2009)

Anaplastic large T-cell lymphomas (ALCL) have been separated in two distinct subtypes based on the presence or absence of translocations involving the *ALK* gene. It is accepted that ALK$^+$ ALCL is a distinct subgroup that shares a unique phenotype, with well defined genetic and clinical features. Although the clinical presentations, translocations, and genetic events vary between ALK$^+$ and ALK$^-$ ALCL, the relationship between these two ALCL subtypes and also whether ALK$^-$ ALCL may represent a subset of peripheral T-cell lymphomas, not otherwise specified (PTCL, NOS) remain unclear. In this regard, the WHO classification classifies ALK$^-$ ALCL as a provisional entity. A better understanding of the underlying genetics would provide critical explanations to answer some of these questions. With the aim of identifying the genetic events underlying the pathogenesis of ALCL, we studied a series of 69 cases of ALCL (34 ALK$^-$, 35 ALK$^+$) with high-density genome wide SNP-based arrays.

Material and methods

DNA was extracted from frozen biopsies. DNA profiles were obtained using the Affymetrix GeneChip Human Mapping SNP6 arrays. Differences in frequencies between subgroups were evaluated using Fisher's exact test. A subset of cases also had available gene expression profiles. Clinical data were available in half of the cases, and genomic lesions were evaluated for their impact on clinical outcome with the log-rank test.

Results

The most common losses were at 6q21, 17p13 (19%), 13q22.3 (15%), 3p21.31, 13q32.3 (14%), 1p13.3, 16q23.1 (*WWOX*) (13%), 16q23.3–24.1 (12%), 1p33 and 16q22.1 (10%). The most common gains occurred at 8q22 (20%), 1q (13%), 7q (10–15%; CDK6, 15%), 8q24, and 9p24.1 (10%). ALK$^-$ ALCL displayed a higher number of genomic aberrations in comparison with ALK$^+$ ALCL. The lesions presenting major differences included: –6q21 (35% vs. 6%), –1p13 (26% vs. 3%), –3q22 (26% vs. 0%), –4q12–q26 (18% vs. 0%), +9p21 (17% vs. 0%), –17p13 (TP53, 26% vs. 6%). The deletions at 6q21 targeted the gene *PRDM1*, coding for BLIMP1. The whole coding sequence of *PRDM1* has been sequenced in 33 ALK$^-$ ALCL samples. Only one somatic mutation, inducing a stop codon, was identified, in one case bearing copy neutral loss of heterozygosity (cnLOH) spanning *PRDM1* locus, suggesting a loss of functional protein in this patient. As a whole, 38% of ALK$^-$ ALCL presented loss of at least one allele of *PRDM1*. Only two cases were observed with complete gene loss: the ALK$^-$ case with somatic mutation plus cnLOH, and one ALK$^+$ case with homozygous deletion. The presence of 6q21 deletion had an impact on progression free survival among all ALCL, likely reflecting its association with ALK$^-$ ALCL, but not when considering ALK patients only. Xenografts derived from primary ALCL samples bearing 6q21 loss presented decreased BLIMP1 expression level. The detection of *PRDM1* loss was present also in cell lines in which also a decreased level of BLIMP1 RNA and protein was observed. Additional genes, members of PRDM1 pathway, were identified as targets of focal deletions.

Conclusions

A series of recurrent lesions has been identified in ALCL. Alongside TP53 loss, inactivation of PRDM1 by genomic losses or somatic mutations was the most commonly detected lesion and was more frequently inactivated in ALK$^-$ ALCL. PRDM1, encoding BLIMP1, a master regulator of T-cells differentiation, appears as a central gene in ALCL pathogenesis. Other genes belonging to the same pathway were found to have focal genomic aberrations in a smaller number of cases.

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Bron Luc | **Identifying targets for, as well as overcoming barriers to, specific immunotherapy in human head and neck squamous cell carcinoma**
(OCS 02191-02-2008)

Treatment of head and neck squamous cell carcinoma depends on the stage and location of the primary tumour. Whereas surgery is often proposed for small tumours located in the oral cavity, radiotherapy in combination with chemotherapy is an excellent alternative for advanced tumours and when the anatomical function is compromised by surgery. Despite new treatments combining radiotherapy and chemotherapy and the evolution of surgical approaches, the recurrence rate of head and neck cancer remains high and the chances of full recovery relatively low.

The role of the immune system in host defense against the development of cancer is clearly established. In the early phase of development of cancer, the transformed cells can be eliminated by the immune system. A subset of white blood cells with the ability to kill tumours expressing specific antigens is the main immune defense mechanism against tumours. Anti-tumour vaccines aim at inducing strong responses of killer T-lymphocytes specific for defined tumour antigens.

Our initial results showed that 80% of head and neck squamous cell carcinoma express at least one tumour associated antigen, which can be recognized by killer T-cells. In addition, cancer testis antigens, MAGE-A4 and MAGE-A3, are expressed in over 50% of HNSCC. In parallel, we showed in the peripheral blood of patients with head and neck cancer the presence of T-cells able to recognize and generate a specific immune response against these molecules. These first results confirmed our hypothesis that in this type of cancer, patients develop immune responses against specific tumour.

In a second stage, we developed a phase I clinical trial to immunize patients with head and neck cancer, using a mixture of proteins capable of activating the host immune system. We screened more than 30 patients; however, the drastic criteria for the inclusion of patients allowed us to vaccinate a limited number of patients.

It appears clearly that tumours are often able to evade the immune system. To gain further insight, we performed an immunohistochemical study of 35 head and neck squamous cell carcinoma samples to identify the different actors of these tumour defense mechanisms at the tumour microenvironment. It appears that dendritic cells, critical for the efficient activation of killer T-lymphocytes, were weakly present at the tumour microenvironment. Moreover, tumour cells express molecules such as arginase, or cyclooxygenase-2, which block the activity of killer T-lymphocytes. The presence at the tumour microenvironment of FOXP3$^+$ T-lymphocytes, a subclass of regulatory T-cells, seems to improve the prognosis of patients significantly. The exact role of such cells remains unclear, but certainly these results confirm the importance of the immune system in the patient's clinical evolution.

Immunotherapy alone may not by itself have a chance of curing the tumour. Rather, a combination of conventional radiotherapy and chemotherapy with immunotherapeutic approaches appears to be the future direction. In general, a large proportion of head and neck squamous cell carcinomas resist radiotherapy and/or chemotherapy treatments. We are also currently studying these mechanisms of resistance to better understand and try to identify potential targets in order to develop new vaccination strategies against tumour cells that escape the first line of treatment. The destruction of resistant tumour cells and the increase of the response rate against those treatments will undoubtedly lead to a marked improvement in survival of patients with squamous cell carcinoma of the head and neck.

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Bubendorf Lukas | **Detection and isolation of novel gene fusions in carcinomas by high-resolution genomic profiling** (OCS 02285-08-2008)

The majority of human malignant tumours are characterized by chromosomal instability. This instability includes the accumulation of genomic aberrations, like deletions, amplifications, mutations, and translocations. The involvement of two genes in the latter rearrangement can lead to the generation of so-called gene fusions. The resulting protein product of these gene fusions can be of chimeric nature and thus be highly specific for the tumour. Due to this high specificity, these proteins are favourable drug targets for a novel generation of specific drug therapies in cancer.

The aim of this study was the further development and the application of a methodology to detect and isolate novel gene fusions in solid tumours. Furthermore, the technology should be further developed in order to be able to separate and sort the distinct clonal populations present within a tumour and apply genomic profiling technologies, such as array-CGH, to these populations.

In this study, we were able to detect several novel gene fusions. These fusions and their resulting protein products will be verified and validated for their biological and clinical significance in continuative projects. Further, we were able to further develop the technology mentioned above. We are now able to detect and sort the distinct clonal tumour populations of archived tumour specimens by usage of a high-end flow sorter. The sorting and thus the separation of these populations now allows for the genomic profiling of the pure individual clonal tumour populations. The application of high-resolution genomic analysis methods to these pure populations led to the detection of minute genomic aberrations at a resolution that was hitherto not possible with conventional technologies. We applied this technology to different tumour specimens from different time points originating from the same patients, and we were able to infer the clonal composition and the genomic evolution of the analysed tumours. This is of fundamental importance in order to understand which genomic aberrations were responsible for the growth of those tumours and thus may represent their targets of vulnerability. Thus, the protein products that result from these aberrations can be regarded as highly attractive targets for novel target-specific cancer therapies. We are convinced that the further application of our methodology and the resulting findings will contribute to the development of personalized approaches for cancer treatment in the near future.

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Cathomas Gieri | **The role of polyomavirus in the development of Merkel cell and epithelial skin carcinomas** (KLS 02392-02-2009)

Merkel cell carcinoma is a rare but aggressive neuroendocrine tumour of the skin. Recently, it has been shown that in about 80 % of these tumours a new virus, a polyomavirus called Merkel cell polyomavirus (MCV), can be detected.

In this study, a number of Merkel cell carcinomas were analysed by fluorescence *in situ* hybridization (FISH), immunohistochemistry, and PCR. In about 60 % of tumours, MCV could be detected by FISH in the tumour cell genome; a similar number of tumours show viral protein expression, namely, expression of the large T-antigen, although only a partial concordance was observed. Further analyses by quantitative PCR and detection of DNA mutations in the viral genome showed that two types of viral persistence in Merkel cell carcinomas may exist. These differences in persistence may represent a timely development of Merkel cell carcinomas. Finally, a small group of Merkel cell carcinomas is not associated with MCV.

In the second part of the project, squamous and basal cell carcinomas of the skin of immunocompetent and immunocompromised patients were analysed. Using PCR, in about one-third of these tumours, MCV could be detected, namely, significantly more often in basal cell carcinomas in comparison to a control collective. Further analyses showed, however, that only in less than 2 % a weak viral protein expression could be seen, and also no viral integration in the cellular genome could be detected by FISH. Finally, in the basal cell carcinoma analysed, no specific viral gene mutation was observed.

Our data confirm the strong correlation between Merkel cell carcinoma and the Merkel cell polyomavirus (MCV). In addition, the data suggest different ways of viral persistence in the tumours, a finding which may be of importance in future therapeutic or prophylactic procedures. On the other hand, our data show that in other common epithelial skin tumours, the basal cell carcinomas and the squamous cell carcinomas, MCV is unlikely to be involved in the pathogenesis. The detection of viral DNA in these tumours by PCR may be a surrogate marker of a diminished immunocompetence. In view of the similar risk profile in these epithelial tumours in comparison to the Merkel cell carcinoma, the question remains unresolved whether a viral aetiology may be involved in the pathogenesis of these common epithelial skin tumours.

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Chappuis Pierre Olivier | **Prospective screening for hereditary nonpolyposis colorectal cancer (HNPCC) syndrome in a population-based setting**
(OCS 02073-04-2007)

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, is the major cancer predisposition syndrome, accounting for about 2–5 % of all colorectal and endometrial cancers. Germline mutations in four genes (MLH1, MSH2, MSH6, PMS2) are responsible for Lynch syndrome. Individuals carrying germline mutations in these genes have a very high lifetime risk for developing colorectal and endometrial cancer, typically at an earlier age than sporadic cancer diagnosed in the general population. Mutation carriers have also a moderately increased risk for some other malignant tumour types. Regular screening in mutation carriers has a strong impact on cancer-specific survival.

Aims

The main objective of this project is to develop, implement and test a strategy based on a pre-screening of colorectal and endometrial cancers diagnosed in the cantons of Geneva and Valais before the age of 75 years, in order to identify carriers of germline mutations in genes responsible for Lynch syndrome in a population-based setting. Lynch syndrome-related tumours demonstrate a salient signature on tumour tissue samples, i.e. microsatellite instability and lack of expression of several proteins revealed by immunohistochemistry. Up to 10–15 % of sporadic colorectal and endometrial cancers demonstrate similar characteristics.

Methodology

All clinicians, both in private practice and in hospitals, involved in the management of colorectal and endometrial cancer patients in the cantons of Geneva and Valais were informed about this project. These clinicians informed their patients and let us know how to contact them. After obtaining written consent and taking an interview-based personal and familial medical history, incident cases of invasive colorectal and endometrial cancer diagnosed before the age of 75 years are eligible for a pre-screening procedure on tumour tissue in a centralized laboratory. In the case of positive results, genetic counselling is proposed, and selective testing for germline mutations in genes involved in Lynch syndrome is discussed.

Main results

Up to March 31, 2012, 226 patients were selected in the cantons of Geneva and Valais and 218 (164 colorectal cancer and 54 endometrial cancer cases) were eligible for this study. Up to now, 13 % (23/177) had positive prescreening results. Except for two patients, all had genetic counselling. For 13 individuals, genetic testing has been done, and four have been identified as carriers of pathogenic germline mutations in one of the genes involved in Lynch syndrome (MLH1:2, MSH2:1, PMS2:1). Thus, 2.3 % (4/177) of the cases in this cohort is related to Lynch syndrome. It is noteworthy that two out of these four situations do not fulfil any of the international criteria or guidelines proposed to identify Lynch syndrome.

Significance for the patients

Use of the current clinical criteria and guidelines to identify Lynch syndrome is probably insufficient in unselected patients with colorectal and endometrial cancer. Prescreening to demonstrate the presence of several characteristics on cancer tissue samples, i.e. loss of expression of some proteins by immunohistochemistry and search for microsatellite instability, could be considered prospectively for a better identification of Lynch syndrome in the general population. To consolidate this conclusion, this study should be prolonged for an additional year.

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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)

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma in humans. It usually shows an aggressive clinical course. However, there is marked inter-individual clinical and pathological heterogeneity. By the use of the currently most effective therapeutic strategies about 60 % of the patients can be cured. Unfortunately, up to now it is not possible to use specific biologic features of tumour cells (called "biomarkers") to assess the prognosis or to predict response to therapy of an individual patient. 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) to identify prognostic and predictive biomarkers.

Study design
Our main objective was to identify robust and reproducible prognostic and predictive biomarkers in DLBCL patients in order to apply a most effective, individualized therapy in the future.

Methods
We prospectively analysed the expression of various biomarkers at the level of individual tumour cells using immunohistochemistry in 124 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 clinical-pathological parameters and the clinical course of the patients.

Results
The patients' median age was 59 years; 68 were men, 56 women. BCL2-gene breaks were observed in 11 % of cases and those cases express the Bcl2-protein in 95 % of tumour cells as compared to 43 % in non-rearranged cases. C-MYC breaks were observed in 10 % of the cases. Only one-third displayed C-MYC/IGH fusions. A complete response (CR) was achieved in 90 out of 117 patients. Molecular factors (biomarkers) that were linked to failure to achieve a CR were CD5-positivity, EBER-positivity (EBV infection of tumour cells), and presence of either BCL2 or C-MYC gene rearrangements.

Benefit for the patients
Despite recent progress in the therapy of DLBCL by immunochemotherapy, up to 40 % of the patients show a relapse (or initial treatment failure). Thus, it is important to identify these patients already during first diagnosis of their disease to optimize treatment strategies from the beginning. Besides clinical factors such as patient age, tumour stage, and performance status, tumour-specific factors (biomarkers) are considered important. In our study we identified four biomarkers (CD5-protein expression, EBV infection, translocation of the BCL2 or C-MYC gene) that are associated with treatment failure using a standard therapy for DLBCL. These results are the basis for future prospective analyses with larger patient cohorts and the development of individualized therapies of DLBCL.

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Forrer Flavio | **Glucagon-like peptide 1 (GLP-1) receptor targeting a novel method for cancer imaging: Design, synthesis, preclinical and clinical evaluation of radiolabelled GLP-1 chelator conjugates** (OCS 02259-08-2008)

Insulinoma are rare, mostly benign tumours that mainly occur in the pancreas. Due to their characteristic of unregulated secretion of insulin, life-threatening hypoglycemia may occur. The therapy of choice is the surgical removal of the insulinoma.

As insulinoma are often very small, presurgical detection using conventional radiological methods (such as CT, MRI or endoscopic ultrasound) is challenging and often fails. Insulinoma consistently overexpress glucagon-like peptide 1 (GLP-1) receptors. Hence, these tumours can be detected preoperatively using GLP-1 receptor scintigraphy. This facilitates presurgical planning, and it confirms the clinically suspected diagnosis of insulinoma. Exendin-4 binds to GLP-1 receptors. The newly developed radiopharmaceutical Exendin-4 labelled with the diagnostic radionuclide Indium-111 allows scintigraphic *in vivo* detection of GLP-1 receptors, i.e. insulinoma.

The goal of this study was to evaluate the clinical value of the newly developed GLP-1 receptor scintigraphy in patients clinically highly suspicious for insulinoma.

23 patients (age 30 to 70 years) with biochemically proven endogenic hyperinsulinemic hypoglycemia, i.e. highly suspicious for insulinoma, were included. The patients were injected with 100 MBq of In-111-Exendin-4. Planar whole body scans as well as SPECT/CT images of the abdomen were acquired four hours and four to six days after injection. The results were compared to the intraoperative findings with regard to histology and localization of the insulinoma. Additionally, the scintigraphic results were compared with the other diagnostic procedures that the patients underwent previously.

The sensitivity for the GLP-1 receptor scintigraphy was found to be close to 94 %. In two cases the GLP-1 receptor scintigraphy was the only method that was capable of detecting the tumour preoperatively. In three cases, besides the GLP-1 receptor scintigraphy, the invasive procedure selective venous sampling was the only method to be positive, and in two cases the endoscopic ultrasound was the only method that was positive besides the GLP-1 receptor scintigraphy.

In all patients with positive GLP-1 receptor scintigraphy and intraoperatively proven insulinoma an agreement in localization of the tumour was found (100%).

Our study proves GLP-1 receptor scintigraphy using In-111-Exendin-4 to be a very accurate method with a sensitivity of almost 94% for the preoperative localization of insulinoma. In contrast to other highly sensitive methods, such as selective venous sampling or endoscopic ultrasound, GLP-1 receptor scintigraphy is not invasive, and it allows a more precise localization of the tumour. Additionally, ectopic or multiple insulinoma can be detected.

We believe that in the future, GLP-1 receptor scintigraphy will become the gold standard for the preoperative localization of insulinoma.

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Frattini Milo | **Identification and characterisation of predictive molecular markers in colorectal cancer patients treated with EGFR-targeted therapies**
(OCS 02301-08-2008)

Colorectal cancer (CRC) is the second leading cause of cancer-related death in Western countries. Newer therapeutic options for treating advanced CRCs include targeted biologic therapies, especially monoclonal antibodies (MoAbs) against EGFR. These MoAbs have shown efficacy in about 10–20% metastatic colorectal cancer (mCRC) patients. It is now emerging that genetic alterations of EGFR and its downstream signalling effectors may predict the efficacy of EGFR-targeted drugs. The role of KRAS as negative predictor of anti-EGFR drugs' efficacy is well established. KRAS mutations, however, only account for 30–40% of non-responsive patients.

Objective
The overall goal of this research proposal was to better understand the significance of deregulation of EGFR (the target), of proteins of its downstream signalling cascade (NRAS, BRAF, PIK3CA, PTEN), and of other targets linked to the EGFR pathway (HER2, TOPK) for response to EGFR-targeted therapies in CRC patients.

Methods and procedure
A series of patients affected by a mCRC were identified in Ticino and then treated with cetuximab or panitumumab. Patients' tissue specimens were evaluated for EGFR and HER2 gene status by fluorescent *in situ* hybridization (FISH), for PTEN and TOPK protein expression by immunohistochemistry, and for KRAS, NRAS, BRAF and PIK3CA mutational status by direct sequencing.

Results
In our cohort, we found that a normal gene status of EGFR, the presence of KRAS mutations, BRAF mutations, PIK3CA mutations and the PTEN loss of expression, all represent independent predictive markers of resistance to EGFR-targeted therapies, because they occurred only in patients who experienced no response to these drugs. In addition, we demonstrated that not all mutations occurring in KRAS and PIK3CA gene exert the same effect on drug efficacy. At the end, we demonstrated that also the analysis of HER2 gene status and TOPK expression may help in the identification of patients resistant to EGFR-targeted therapies.

Recommendations or benefits for patients
The data generated by these research proposals will help to clarify possible interplays between specific genetic alterations in EGFR activation pathways and anti-EGFR drugs' efficacy. In particular, the determination in tissue samples of molecular alterations able to predict the efficacy of EGFR-targeted therapies may provide important information for tailoring adjuvant chemotherapeutic regimes, avoiding inefficacious treatments, and maintaining the costs related to the clinical use of these novel drugs under control.

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Körner Meike | ***In vitro* evaluation of the glucagon-like peptide 2 receptor expression in human cancer: molecular basis for *in vivo* tumour radiotargeting**
(OCS 02349-02-2009)

Receptors for small proteins (peptides) are often highly overexpressed in human tumours. This represents the molecular basis for important clinical applications in tumour patients, namely, for *in vivo* receptor targeting of tumours, where the tumoural peptide receptors are the molecular targets for pharmacological peptide analogues. Administration of radioactively labelled peptide analogues leads via specific receptor binding to an accumulation of radioactivity within the tumour, allowing for either radiographic tumour imaging or radiation therapy. Furthermore, non-radioactive peptide analogues can interfere with receptor-controlled tumour functions such as hormone secretion of growth.

The glucagon-like peptide 2 (GLP-2) receptor represents a potential new candidate for such applications. It is closely related to the glucagon-like peptide 1 (GLP-1) receptor, which has recently been identified to be an important clinical target in insulin producing tumours. The GLP-2 receptor has so far been of clinical interest for its regulatory role in intestinal growth and inflammation and, consequently, its potential as therapeutic target for the GLP-2 analogue teduglutide in short bowel syndrome and Crohn's disease. Recently, evidence has emerged on an additional possible role of the GLP-2 receptor in cancer. Indeed, the GLP-2 receptor was identified in tumours in single instances. Moreover, *in vitro* data indicate that it may stimulate tumour cell migration and growth. These preliminary results call for an in-depth evaluation of the GLP-2 receptor for its suitability as tumour target.

The aim of our project was to perform the first step in such an evaluation, namely, to assess GLP-2 receptor expression quantitatively in a large spectrum of human tissues including tumours.

We analysed 385 human tissue samples for their GLP-2 receptor expression with *in vitro* receptor autoradiography. This method identifies receptor binding sites in tissues. It allows specific receptor identification based on receptor pharmacology as well as quantification of receptor levels in tissues. We thus found a marked GLP-2 receptor expression in selected tumour types, namely, at high levels in gastrointestinal stromal tumours (GIST) and rarely in rhabdomyosarcomas. These binding data were confirmed with RT-PCR. Moreover, a significantly increased GLP-2 receptor expression was identified in the gut nerve plexus in Crohn's disease.

In conclusion, GLP-2 receptor expression in GIST represents the molecular basis for an *in vivo* GLP-2 receptor targeting of these tumours. Moreover, the GLP-2 receptors in the gut nerve plexus may represent a molecular target for teduglutide in Crohn's disease.

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Kristiansen Glen | **Identification of a clinically applicable prognostic RNA signature of prostate cancer** (KFS 02465-08-2009)

In Switzerland, on average 5,815 new prostate cancers are diagnosed and 1,285 men die as a consequence of prostate cancer per year. More than 50 % of prostate cancers are graded with an intermediary Gleason score (6–7), for which it is currently difficult to make a prognosis and to choose adequate treatment. These patients often suffer the adverse effects of the treatment without a benefit. Therefore, sensitive and specific diagnostic and prognostic tools are urgently needed to improve the prognosis of cancers with intermediate Gleason scores. This study aims to provide a new approach to classify prostate risk by RNA signatures.

Methods and results

Gene expression signatures lend themselves for prognosis as quantifiable, reproducible and objective measures of the molecular pathological condition of a tissue. First, we validated the Nanostring technology, a new method that measures target mRNA directly without enzymatic reactions, for reproducibility, sensitivity and its robustness towards partially degraded RNA extracted from formalin-fixed paraffin-embedded (FFPE) tumour samples and confirmed that Nanostring is a suitable method to measure gene expression on partially degraded RNA. For further analysis, control-gene normalization based on five endogenous control genes was used, as the same genes can be used for normalization in follow-up real-time PCR experiments. With these, we measured the expression of 159 genes using Nanostring in 96 FFPE tumour samples. We identified six genes that significantly predicted biochemical relapse in radical prostatectomy patients in univariate Cox regression models. High expression of three genes correlated with good prognosis, whereas high expression of three other genes correlated with poor prognosis. Two genes could be combined in a molecular score able to predict biochemical relapses with a sensitivity of 94 % and a specificity of 67 %. Ten years relapse-free survival was over 95% for patients with a high score and less than 50 % for patients with a low score.

Conclusions

The inclusion of the molecular score significantly improved prognosis in a multivariate model containing preoperative PSA levels. The results are currently being validated in a larger cohort.

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Mamot Christoph | **Prospective evaluation of the predictive value of PET in patients with diffuse large B-cell lymphoma under R-CHOP-14, a multicentre study** (OCS 02270-08-2008)

Metabolic imaging by FDG-PET provides functional tissue characterization and has been used in patients with various lymphomas in the past. Early assessment of therapeutic response by a robust imaging tool is potentially useful in order to stratify patients for risk-adapted tailored therapy strategies. Our main objective was to determine the prognostic impact of FDG-PET after two cycles of R-CHOP-14, prospectively and under standardized conditions.

Patients with any stage of diffuse large B-cell lymphoma were treated with six cycles of R-CHOP-14, followed by two cycles of rituximab. FDG-PET exams were performed prior therapy, after two cycles of R-CHOP-14, after four cycles of R-CHOP-14 (if positive PET after two cycles), and at the end of treatment. The primary endpoint was event-free survival (EFS) at two years. Secondary endpoints include EFS, overall survival, overall response, PET results, and histological results of PET positive lesions after treatment. A positive PET was defined as a measurable and evaluable lesion(s) with a SUVmax (lesion) > SUVmax (blood pool). PET exams are evaluated locally and by central review.

Between January 2008 and May 2010 a total of 156 patients with untreated DLBCL were prospectively enrolled in the trial. By December 2010, first data from 114 patients were available. Median age was 60 years, with a WHO performance status of 0 in 55 %, PS1 in 37 %, and PS2 in 8 % of cases. According to the International Prognostic Index (IPI), low risk was found in 54 patients (49.5 %), low-intermediate risk in 22 (20 %), high-inter-

mediate risk in 18 (16.5%), and high risk in 15 (14%). PET exams from all patients before and after two cycles of R-CHOP-14 are available for this analysis, and 51 patients had an additional PET exam after four cycles. 61% of PET exams were defined as positive after two cycles by local institution. Seventy-one of these exams remained positive after four cycles of therapy, and 29% changed to negative. 100% of patients with a negative PET after two cycles reached a complete response at the end of treatment. For PET positive patients a CR was reached in 51, respectively. Data on EFS at two years are not mature at the time of first analysis.

We conclude that before therapy decisions for patients with DLBCL can be made by PET, standardized studies such as this one have to confirm the ability to stratify patients to different risk groups reliably.

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Schwaller Jürg | **Exploring new molecular therapeutic targets in MLL-X acute leukaemia**
(OCS 02357-02-2009)

Expression of mixed lineage leukaemia (MLL)/lymphoma fusions is a hallmark for a significant group of *de novo* paediatric and adult and therapy-related acute leukaemia with a poor prognosis. Previous work has suggested that the MLL fusions act as aberrant transcriptional regulators and are essential to induce and probably also maintain acute leukaemia. Genetic studies have identified potential cellular cofactors as well as downstream effectors of MLL fusions including protein kinases like *FLT3* or *PIM1*.

We addressed the role of PIM kinases as biomarkers and therapeutic targets in MLL-fusion leukaemia and other haematological malignancies. We found increased expression of *PIM1* and *PIM2* in leukaemic blasts as well as in the majority of cases of high large lymphomas. In high-grade lymphoma, PIM overexpression and in particular nuclear expression of *PIM1* correlated with the stage of the disease, but several tumour cell lines were rather resistant to small molecule PIM kinase inhibitors. In contrast, PIM kinase inhibitors significantly impaired the growth of cell lines and primary acute leukaemic blasts. Interestingly and rather unexpectedly, we found that

PIM1 affects the homing and migration of leukaemic cells by regulating the surface expression of the CXCR4 chemokine receptor by phosphorylation of the serine 339 (CXCR4-S339) in the intracellular tail. We established model systems that made it possible to demonstrate that uncontrolled phosphorylation of CXCR4-S339 not only increased cellular adhesion *in vitro* but also impaired the release of leukaemic cells from the bone marrow niche *in vivo*. To search for additional potentially drugable kinase targets we established a high-throughput knockdown screen in primary cells from transgenic mouse models of MLL-fusion gene acute leukaemia. In parallel, we explored the possibility to impair MLL-fusion mediated transformation by disrupting critical protein-protein interactions within the MLL complex. In addition, we evaluated the anti-leukaemic potential of several novel small molecules that interfere with the aberrant transcriptional activity of the MLL-fusions. Our work so far not only discovered a novel potentially drugable signalling pathway regulating homing, adherence, and migration of leukaemic cells but also provided essential insights for development of novel molecularly targeted therapeutics against acute leukaemia.

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Speiser Daniel E. | **Immunotherapy of melanoma patients and analysis of the regulation of tumour antigen-specific CD4 and CD8 T-cells**
(OCS 02279-08-2008)

Cancer-specific immune cells, i.e. the "killer" T-cells, can effectively destroy tumours, as demonstrated with T-cells directly after isolation from circulating blood of cancer patients. In the tumour microenvironment, however, these same T-cells show much reduced anti-cancer activity, indicating that cancer tissues induce local immune deficiency. It is important to identify the underlying mechanisms based on which novel therapies can be developed.

The reasons for T-cell deficiency have primarily been characterized in chronic viral diseases. As compared to cancer-specific T-cells, virus-specific T-cells are more frequent and more active, which also makes them much more accessible for research. Recent studies demonstrated that T-cells in mice with chronic viral infection are "exhausted", as they have lost the capability to eliminate viruses. Subsequently, similar findings in humans showed that T-cell exhaustion was responsible for the lack of T-cell mediated protection against human immunodeficiency virus (HIV) or hepatitis C virus (HCV). These results strongly promoted the understanding of human immune deficiencies causing frequent infectious diseases.

Until recently, much less was known about mechanisms of T-cell deficiency in cancer patients. To obtain comprehensive information about cancer-specific T-cells, we asked melanoma patients for permission to analyse their T-cells. Upon written informed consent, we performed gene expression profiling of antigen-specific T-cells *ex vivo,* i.e. directly after their isolation from patients. We isolated and sorted such T-cells from 19 melanoma patients and from four healthy donors. First, T-cells were isolated from peripheral blood, after treatment of patients with a powerful cancer vaccine that we had developed recently. And second, we recovered T-cells from the patients' metastases, enabling the analysis of cancer-specific T-cells from the tumour microenvironment. By comparing the cancer-specific T-cells from blood versus metastases, we found differential expression of 332 genes. These genes significantly matched the genes characteristic for T-cell exhaustion in chronic viral infections. Therefore, our study was able to demonstrate that T-cells in metastases are "exhausted", similar to T-cells in chronic viral infections. In addition, our analysis showed that the molecular features of T-cell exhaustion were shared by most patients. These results were remarkable, given the high genetic heterogeneity in humans.

Our data represent the first comprehensive molecular characterization of functional T-cell impairment in cancer tissue of any species and provide a mechanistic explanation for T-cell immune deficiency in cancer. Moreover, our findings propose new opportunities to identify essential disease pathways and novel drug targets. Our data also demonstrate that exhaustion of cancer-specific T-cells is largely reversible. This is very promising, because it means that the T-cells keep their potential to destroy cancer cells, a fact that can be exploited therapeutically. For the future, research will follow the strategy of using powerful vaccination for activating the T-cells systemically, combined with medications that intervene with the identified immune deficiency mechanisms in the tumour microenvironment. Indeed, recent data suggest that this strategy improves the well-being of melanoma patients.

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List of approved research projects in 2011

Total funds allocated: CHF 4,555,000.–

Bodis Stephan | KFS 02779-02-2011 | CHF 195,500.–
Institut für Radio-Onkologie, Kantonsspital Aarau, Aarau
Pilot study to assess the feasibility and toxicity of preoperative external beam radiotherapy for glioblastoma multiforme

Boulay Jean-Louis | KLS 02765-02-2011 | CHF 196,500.–
Departement Biomedizin, Universitätsspital Basel, Basel
Molecular mechanisms of glioma cell invasion

Carbone Giuseppina | KFS 02869-08-2011 | CHF 136,200.–
Laboratorio di oncologia sperimentale, Istituto oncologico della Svizzera italiana (IOSI), Bellinzona
Identification and clinical relevance of microRNA networks regulated by ETS transcription factors in prostate cancer

de Leval Laurence | KFS 02860-08-2011 | CHF 302,800.–
Institut universitaire de pathologie (IUP), Centre hospitalier universitaire vaudois et Université de Lausanne (CHUV-UNIL), Lausanne
Characterization of molecular biomarkers relevant to the biology, diagnosis and prognosis of peripheral T-cell lymphomas

Derré Laurent | KLS 02744-02-2011 | CHF 191,400.–
Unité de recherche en urologie, Centre hospitalier universitaire vaudois (CHUV), Lausanne
Role of the inhibitory receptor BTLA in antigen presenting cells from melanoma and bladder cancer patients: importance of a novel dendritic cell subset

Dummer Reinhard | KFS 02781-02-2011 | CHF 197,800.–
Dermatologische Klinik, UniversitätsSpital Zürich, Zürich
Functional genomics of cutaneous lymphoma

Eychmüller Steffen | KFS 02848-08-2011 | CHF 140,000.–
Palliative Care, Inselspital, Universitätsspital Bern, Bern
Diagnosing dying: development of a tool for identifying the last days of life (LDoL)

Ghadjar Pirus | KFS 02777-02-2011 | CHF 274,900.–
Universitätsklinik für Radio-Onkologie, Inselspital, Universitätsspital Bern, Bern
Dose-intensified salvage RT in biochemically relapsed prostate cancer without macroscopic disease: a randomized phase III trial (SAKK 09/10)

Joerger Markus | KFS 02838-08-2011 | CHF 40,500.–
Fachbereich Onkologie/Hämatologie, Kantonsspital St. Gallen, St. Gallen
Clinical activity of tamoxifen in postmenopausal patients with locally advanced or metastatic ER-positive breast cancer by endoxifen concentrations and pharmacogenetics

Kalberer Christian | KFS 02872-08-2011 | CHF 188,800.–
Diagnostische Hämatologie, Universitätsspital Basel, Basel
In vitro expansion of human natural killer cells under good manufacturing practice conditions for immunotherapy of haematopoietic malignancies

Marra Giancarlo | KFS 02739-02-2011 | CHF 329,100.–
Institut für molekulare Krebsforschung, Universität Zürich, Zürich
The epigenome of colorectal transformation: from early tumours to liver metastases

Pless Miklos | KLS 02745-02-2011 | CHF 145,800.–
Medizinische Onkologie, Kantonsspital Winterthur, Winterthur
Preoperative chemoradiotherapy vs. chemotherapy alone in non-small cell lung cancer patients with mediastinal lymph node metastases (stage IIIA, N2): a randomized prospective phase III trial (protocol SAKK 16/00)

Pruschy Martin | KLS 02788-02-2011 | CHF 317,400.–
Labor für molekulare Radiobiologie, Klinik für Radio-Onkologie, UniversitätsSpital Zürich, Zürich
Targeting of ionizing radiation-activated treatment resistances: radiation-induced para- and autocrine factors

Roosnek Eddy | KFS 02830-08-2011 | CHF 249,900.–
Service d'hématologie, Hôpitaux universitaires de Genève (HUG), Genève
Novel methods to quantify inflammatory disease and immunity to adjust therapeutical interventions in patients after haematopoietic stem cell transplantation

Ruiz Christian | KFS 02780-02-2011 | CHF 196,500.–
Institut für Pathologie, Universitätsspital Basel, Basel
Comprehensive analysis of the genomic evolution of clonal populations in the progression of hormone-sensitive prostate and breast cancers

Schanz Urs | KFS 02858-08-2011 | CHF 169,900.–
Klinik für Hämatologie, UniversitätsSpital Zürich, Zürich
EBMT HCT vs CT in elderly AML: a randomized phase III study comparing conventional chemotherapy to low dose total body irradiation-based conditioning and haematopoietic cell transplantation from related and unrelated donors as consolidation therapy for older patients with AML in first complete remission

Schwenkglenks Matthias | KLS 02757-02-2011 | CHF 217,400.–
Institut für pharmazeutische Medizin, Universität Basel, Basel
A health economic cost-utility analysis alongside the randomized controlled clinical trial SAKK 75/08: multimodal therapy with and without cetuximab in patients with locally advanced oesophageal carcinoma: an open-label phase III trial

Speiser Daniel E. | KFS 02836-08-2011 | CHF 343,700.–
Clinical Tumor Biology & Immunotherapy Unit, Centre Ludwig de l'Université de Lausanne pour la recherche sur le cancer, Hôpital Orthopédique/CHUV, Lausanne
Characterization of T-cell activation and suppression in melanoma patients by ex vivo analysis of myeloid, lymphoid and tumour cells

Terracciano Luigi M. | KFS 02867-08-2011 | CHF 196,500.–
Institut für Pathologie, Universitätsspital Basel, Basel
Dissecting the role of HOXA13 in hepatocarcinogenesis

Vassella Erik | KFS 02826-08-2011 | CHF 204,400.–
Institut für Pathologie, Universität Bern, Bern
Role of microRNAs in regulating EGFR signalling and cytotoxicity induced by receptor tyrosine kinase inhibitors in non-small cell lung cancer

Zucca Emanuele | KFS 02859-08-2011 | CHF 320,000.–
Istituto oncologico della Svizzera italiana (IOSI), Ospedale San Giovanni, Bellinzona
A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of mediastinal radiotherapy after rituximab-containing chemotherapy to patients with newly diagnosed primary mediastinal large B-cell lymphoma (PMLBCL)

Approved bursaries in 2011

Total funds allocated: CHF 263,400.–

Kim Corina | BIL KFS 02806-08-2011 | CHF 67,000.–
Sympathetic nervous system regulation of pancreatic cancer progression
Destination: Peter MacCallum Cancer Center, Monash University, Melbourne, Australia

Negretti Laura | BIL KFS 02807-08-2011 | CHF 13,900.–
Postgraduierter Lehrgang in Sexualmedizin und Sexualtherapie
Destination: Abteilung gynäkologische Sozialmedizin und Psychosomatik, Frauenklinik, Universitätsspital Basel, Basel

Soldini Davide | BIL KLS 02790-02-2011 | CHF 54,500.–
Study of the role of cell competition in human neoplastic diseases
Destination: Hammersmith Hospital, Imperial College, London, United Kingdom

Templeton Arnoud | BIL KFS 02805-08-2011 | CHF 128,000.–
Clinical and research fellowship genitourinary oncology
Destination: Princess Margaret Hospital and University of Toronto, Toronto, Canada

Presentation of approved research projects in 2011

Bodis Stephan | **Pilot study to assess the feasibility and toxicity of preoperative external beam radiotherapy for glioblastoma multiforme**
(KFS 02779-02-2011)
Duration: 01.07.2011–01.07.2013

Glioblastoma multiforme is one of the most aggressive brain tumours, with a median survival of less than a year. Radiotherapy increases time to local recurrence; however, current postoperative radiotherapy lasts six weeks. This clinical phase I study tests the role of preoperative, short-term radiotherapy of 5 gray daily for five days. Integrated in this research proposal is functional imaging, including tractography and functional MRI of critical brain areas. These neuroradiological findings will be integrated step by step in our radiotherapy planning. A similar strategy was successfully established for rectal cancer 15 years ago.

Study goals
1. Feasibility of preoperative radiotherapy over one week with a daily dose of 5 Gy
2. Integration of neuroradiological functional imaging in radiotherapy planning
3. Research for prognostic or predictive factors for further dose optimization in preoperative radiotherapy, possibly in combination with chemotherapy

Material and methods
Patient cohorts of five patients each will be treated with increasingly intensive, preoperative radiotherapy, at later steps eventually combined with chemotherapy. The local ethics committee (canton of Aargau) will be informed after each cohort and will decide if a next cohort can be included in this ongoing step by step phase I study.

Potential gain for patients
Assumed that this preoperative radiotherapy regimen is equivalent to the current postoperative standard radiotherapy, radiation will be decreased from six weeks to one week. With integrated, neuroradiological functional imaging a precise radiotherapy could be offered with selective protection of critical, neurological areas.

Potential long-term gain (visionary goal)
Due to increased knowledge in neuroanatomy and tumour biology, radiochemotherapy, either pre- or postoperative, could be better tailored to the needs of each patient. This could increase both the efficacy of tumour control and treatment tolerance.

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Boulay Jean-Louis | **Molecular mechanisms of glioma cell invasion** (KLS 2765-02-2011)
Duration: 01.09.2011–31.08.2014

Gliomas progress by invasion of adjacent brain tissue by cells detached from the tumour mass. Invasion is assessed by the thickness of the infiltrated zone.

Objectives:Identify molecular mechanisms of invasion by gliomas. Methods and results: Genomic DNA, messenger RNA, and microRNA are extracted from gliomas of defined invasion grade. Candidate genes identified by micro-array analyses are genetically targeted to evaluate their roles in tumour invasion.

We have shown the impact of genetic classification of low-grade gliomas on patient survival. We have defined SOX2 and HEY1 as potential regulators of invasion. Our interest is to identify genes targeted by SOX2, HEY1 and microRNAs associated with invasion.

Patient benefits: The discovery of such invasion mechanisms makes possible molecular diagnostics of invasion and the definition of pharmacological targets for customized therapies.

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Carbone Giuseppina | **Identification and clinical relevance of microRNA networks regulated by ETS transcription factors in prostate cancer**
(KFS 02869-08-2011)
Duration: 01.01.2012–31.12.2013

ETS transcription factors have emerged as important elements in the pathogenesis of prostate cancer. We recently identified specific ETS gene signatures in human prostate tumours and showed that these transcription factors control key genes involved in the pathogenesis and progression of prostate cancer. In these studies, we propose to identify the network of microRNAs that are regulated by ETS factors in prostate tumours. These data will be supplemented by a validation of the biological functions of the microRNAs and identification of their targets. We plan to test also the presence of the identified microRNAs in serum/plasma of prostate cancer patients and evaluate their potential use as diagnostic and prognostic biomarkers. Collectively, by integrating multiple data from functional assay in cell lines with data from prostate cancer patients, these studies are expected to deliver clinically relevant results. In particular, the results of these

studies may lead to the discovery of novel diagnostic, prognostic, and therapeutic strategies for prostate cancer. Therefore, a significant benefit for prostate cancer patients is anticipated.

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de Leval Laurence | **Characterization of molecular biomarkers relevant to the biology, diagnosis, and prognosis of peripheral T-cell lymphomas**
(KFS 02860-08-2011)
Duration: 01.01.2012 – 31.12.2013

T-cell lymphomas are rare and heterogeneous disorders – accounting for less than 10% of all lymphomas and comprising more than 20 entities. They are often aggressive, and the prognosis is dismal. Their pathophysiology is poorly understood, and their diagnosis is often difficult due to a wide histopathological spectrum within each entity and the lack of precise classification criteria. Our project, based on a cohort of 300 T-cell lymphomas subject to multiparameter molecular characterization and associated with clinical annotations aims to develop a cognitive characterization of these neoplasms based on an integrative strategy, taking into account the analysis of genomic (array-CGH) and epigenetic alterations and of the transcriptome (mRNA and microRNA). This research is expected to lead to: (1) identification of novel molecular markers of T-cell lymphomas, allowing for a better classification of these tumours, (2) identification of novel mechanisms of oncogenesis, (3) development of novel diagnostic tools and prognostic factors, and (4) discovery of therapeutic targets.

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Derré Laurent | **Role of the inhibitory receptor BTLA in antigen presenting cells from melanoma and bladder cancer patients: importance of a novel dendritic cell subset** (KLS 02744-02-2011)
Duration: 01.07.2011 – 01.07.2014

Among antigen presenting cells (APCs), it is well known that dendritic cells (DC) play a pivotal role in initiating immune responses. A novel human DC subtype has recently been reported that expresses CD141 and DNRG-1 molecules. These cells are able to efficiently present molecules from microbes to T-lymphocytes and therefore activate the immune system. Besides that, immune responses are tightly regulated by activating or inhibitory receptors, expressed by lymphocytes and also by APCs. Our recent preliminary results showed that vaccination of melanoma patients with a particular adjuvant leads to the sustained expression of an inhibitory receptor named BTLA on B cells and plasmacytoid dendritic cells (pDC). Thus, in this project we plan to determine whether BTLA activation may decrease B cells and pDC functions. Moreover, we will characterize in depth the role and functions of this new human DC subtype expressing CD141 and DNGR-1. We expect results that will likely deliver novel insights into mechanisms of immune responses and provide better rationales for improvements of anti-cancer therapy.

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Dummer Reinhard | **Functional genomics of cutaneous lymphoma** (KFS 02781-02-2011)
Duration: 01.08.2011 – 01.08.2014

Primary cutaneous lymphomas (PCL) represent the most common subgroup of skin lymphomas. Patients with PCL suffer severely from disfiguring lesions, ulcerations, and itch. Using cutting-edge high-throughput methodology, we plan to do gene and protein expression profiling in order to detect new molecular biomarkers for PCL that may represent promising drug targets. In this project, we will use the combination of transcriptome profiling using Human Exon array by Affymetrix and proteome analysis using high resolution 2D-DIGE.

The unique novelty of this project is the integrative analysis of two high-throughput approaches that characterize tumour cell population on two different levels: on the RNA and protein levels. Taking into account the lack of tumour-targeted therapies for cutaneous lymphomas, this study will help to initiate the development of therapeutic strategies targeting the behavior of leukaemic cells and improve the quality of life in PCL and in other related types of malignancies.

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Eychmüller Steffen | **Diagnosing dying: development of a tool for identifying the last days of life (LDoL)**
(KFS 02848-08-2011)
Duration: 01.02.2012–31.01.2014

Many patients and families, especially in hospital settings, are worried about receiving life-prolonging treatment in the last days of life without a reasonable perspective of improvement and instead experiencing further health deterioration ("futile treatment"). Any approach to diagnosing the beginning of the dying phase may contribute positively towards avoiding inappropriate therapeutic measures.

Health care teams face several challenges while "diagnosing dying". Care pathways like the Liverpool Care Pathway (LCP) were developed to offer structure and support when caring for dying patients and their families. However, the initial criteria for starting the LCP have been criticized frequently in daily practice due to the lack of specificity and evidence. Evaluating such criteria by systematic literature research and Delphi expert process was the focus of this research group while participating in an EU project called OPCARE9 (www.opcare9.eu). As the result of that work, no further specification of criteria allowing diagnosis of the last days of life was identified. It is therefore the aim of this research project to highlight various signs and symptoms prospectively through observation and, finally, to develop a clinical tool for diagnosing dying at the bedside. The international collaboration of our group and access to various care settings in several countries will allow not only a multicentre research project but also effective inclusion of the findings in a future version of the LCP for direct clinical use. The aim of the study, finally, is to recognize or "diagnose" as accurately as possible that a patient will die within the next days and then to care most effectively for the patient and family.

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Ghadjar Pirus | **Dose intensified salvage RT in biochemically relapsed prostate cancer without macroscopic disease: a randomized phase III trial (SAKK 09/10)** (KFS 02777-02-2011)
Duration: 01.05.2011–30.04.2013

The randomized trial SAKK 09/10 compares salvage radiotherapy (RT) with 64 Gy vs. 70 Gy without hormonal treatment in patients without macroscopic biochemical recurrence after prostatectomy (ClinicalTrials.gov Identifier: NCT01272050). Patients with two consecutive rises with the final value >0.1 ng/ml or three consecutive rises with a maximal PSA at randomization of 2 ng/ml are eligible. Either three-dimensional conformal RT techniques or intensity modulated RT can be used. Target volume delineation will be performed according to the guidelines of the European Organisation for Research and Treatment of Cancer (EORTC). The trial aims to accrue 350 patients in four countries. The impact on cancer control, toxicity, and quality of life will be analysed. Should the dose intensification be effective, the results of this trial will help to select the appropriate dose for patients with biochemical recurrence after prostatectomy in the future.

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Joerger Markus | **Clinical activity of tamoxifen in postmenopausal patients with locally advanced or metastatic ER-positive breast cancer by endoxifen concentrations and pharmacogenetics**
(KFS 02838-08-2011)
Duration: 01.05.2011–30.04.2013

Deficient enzymatic activation of tamoxifen to the active metabolite endoxifen may impair clinical outcome in breast cancer patients. CYPTAM is the first prospective multicentre study, assessing the predictive value of endoxifen plasma concentrations and tamoxifen pharmacogenetics for clinical activity and tolerability in postmenopausal women with locally advanced or metastatic breast cancer. Main objectives of the study are to show a 15% increase of objective tumour response and a 20% improvement of progression-free survival in patients with a favourable endoxifen profile (i.e., endoxifen plasma concentrations ≥ 90 nM compared to < 90 nM). Blood samples are taken from patients at baseline and during treatment with tamoxifen; adverse events and treatment response are routinely assessed. This validation study contributes substantially to personalized endocrine treatment in breast cancer and will help to improve treatment efficiency in women with breast cancer.

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Kalberer Christian | ***In vitro* expansion of human natural killer cells under good manufacturing practice conditions for immunotherapy of haematopoietic malignancies** (KFS-02872-08-2011)
Duration: 02. 01. 2012 – 01. 07. 2013

Acute myeloid leukaemia (AML) and multiple myeloma (MM) are blood cell malignancies. Despite high dose chemotherapy and haematopoietic stem cell transplantation (HSCT) relapses are frequent. Improved outcome of haploidentical stem cell transplantations in some patients was attributed to the graft-versus-tumour effect of natural killer (NK) cells.

With this research project we will determine the anti-tumour efficacy of adoptive immunotherapy with high doses of activated NK cells and will contribute to the development of innovative combinatorial therapies in the treatment of AML and MM. Our goals are:

1. NK cells will be expanded under good manufacturing practice (GMP) conditions to obtain cell numbers needed to achieve high effector-to-target ratios *in vivo*. For this purpose, the University Hospital Basel built a GMP facility in 2010.
2. In two clinical immunotherapy trials we will evaluate the feasibility, safety, and efficacy of administration of high doses of NK cells in the treatment of AML and MM after HSCT.

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Marra Giancarlo | **The epigenome of colorectal transformation: from early tumours to liver metastases** (KFS 02739-02-2011)
Duration: 01.07.2011–01.07.2014

This translational research project involves high-throughput analyses aimed at characterizing the epigenome of primary colorectal tumours and their liver metastases and close collaboration with the Departments of Visceral and Transplant Surgery, Gastroenterology, and Pathology at University Hospital Zurich. With the aid of these partners, we are collecting samples of normal colonic mucosa, benign and malignant colorectal neoplasms, and colorectal cancer liver metastases. The tissues are subjected to simultaneous genome-wide analyses of chromatin changes (i.e., DNA methylation and histone modifications) and expression of mRNAs (messenger RNAs), miRNAs (microRNAs), and ncRNAs (long non-coding RNAs).

This approach exploits the full potential (and rapidly declining costs) of "next generation" sequencing technologies and will give us a more comprehensive picture of the epigenetic events that contribute to the various steps of colorectal tumourigenesis. These epigenetic signatures should also bring us a step closer to the goal of individualized management of colorectal cancers, with clinically-validated epigenetic biomarkers that can help predict outcomes and responses to treatment.

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Pless Miklos | **Preoperative chemoradiotherapy vs. chemotherapy alone in non-small cell lung cancer patients with mediastinal lymph node metastases (stage IIIA, N2): a randomized prospective phase III trial (protocol SAKK 16/00)** (KLS 02745-02-2011)
Duration: 01.07.2011–01.07.2014

Patients with operable lung cancer can be cured; however, if the lymph nodes surrounding the tumour are affected, the risk of relapse increases dramatically. The results can be improved by preoperative chemotherapy, but it is not known whether additional radiotherapy could further improve the outcome.

This project compares the efficacy of preoperative chemotherapy versus chemotherapy plus radiotherapy in lung cancer patients. The aim of the trial is to improve survival without relapse of lung cancer through radiotherapy. We are conducting a prospective randomized trial with 240 patients in Switzerland. One group receives chemotherapy followed by a surgical intervention, and the other group will have additional radiotherapy before surgery. If we can show the efficacy of this treatment strategy, it will lead to better survival of the affected patients.

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Pruschy Martin | **Targeting of ionizing radiation-activated treatment resistances: radiation-induced para- and autocrine factors** (KLS 02788-02-2011)
Duration: 01.08.2011–01.08.2014

In this mechanistic and efficacy-oriented project, we will identify ionizing radiation (IR)-induced stress mechanisms and probe the intercellular signalling network in response to IR alone and as part of combined treatment modalities in the tumour and the tumour microenvironment. Para- and autocrine factors are released into the tumour microenvironment in response to radio- and chemotherapy-induced DNA damage and treatment-activated intracellular stress responses. During the time course of a fractionated radiation regimen, they thereby modulate the tumour microenvironment, and these processes co-determine the treatment sensitivity of the tumour and eventually treatment outcome.

These studies will directly outline novel targets for combined treatment modalities with IR and represent a novel rationale and concept to identify and overcome IR-treatment thresholds, eventually to be tested in early clinical trials.

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Roosnek Eddy | **Novel methods to quantify inflammatory disease and immunity to adjust therapeutical interventions in patients after haematopoietic stem cell transplantation** (KFS 02830-08-2011)
Duration: 01.02.2012–31.01.2015

Haematopoietic stem cell transplantation (transfer of red and white blood cell precursors) is a well-established therapy for patients suffering from leukaemia or from other haematological diseases. Unfortunately, certain donor cells in the graft may cause severe inflammation, and this adverse effect decreases the patient's defense against bacteria and viruses considerably. It is crucial to intervene prophylactically, but it is virtually impossible to predict which patients are at risk.

With our project, we want to develop novel laboratory methods to predict the start of these infectious complications. Once established, these methods will help physicians to decide how to protect the patient against infections and modify other therapeutic interventions.

As a whole, these tests will contribute to the efficacy of haematopoietic stem cell transplantation as a therapy for patients with haematological malignancies.

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Ruiz Christian | **Comprehensive analysis of the genomic evolution of clonal populations in the progression of hormone sensitive prostate and breast cancers**
(KFS 02780-02-2011)
Duration: 01. 08. 2011–01. 08. 2014

Tumour heterogeneity is a common phenomenon in solid tumours that impacts the morphology as well as the genomic level of a tumour. However, this heterogeneity is not a coincidence but the product of the genomic evolution of the distinct clonal populations within a tumour.

The aim of this study is analysis of how the different clonal populations can grow and propagate over time and under therapeutic pressure. We will apply a methodology that we co-developed to separate and genomically profile the distinct clonal tumour populations from prostate and breast carcinomas. We will specifically focus on matched tumour specimens: either primary tumour and metastasis, or primary tumour and recurrence.

This procedure will allow us to analyse the characteristics of each clonal population and to determine how each population was able to develop and to withstand the applied therapy.

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Schanz Urs | **EBMT HCT vs CT in elderly AML: a randomized phase III study comparing conventional chemotherapy to low dose total body irradiation-based conditioning and haematopoietic cell transplantation from related and unrelated donors as consolidation therapy for older patients with AML in first complete remission** (KFS 02858-08-2011)
Duration: 12. 07. 2011–11. 07. 2014

Study design
Two-armed, controlled, randomized, open, multicentre, phase III trial: Haematopoietic stem cell transplantation (HCT/SCT) after reduced intensity conditioning or conventional chemotherapy as a consolidation treatment for elderly (≥60 ≤75 years) patients with acute myeloid leukaemia (AML) in first complete remission.

Study aims
Primary objective: Efficacy of allogeneic related or unrelated haematopoietic cell transplantation (HCT) after reduced intensity conditioning as a consolidation treatment for elderly patients with AML in complete remission. Secondary objectives: Safety and toxicity of allogeneic related and unrelated haematopoietic cell transplantation (HCT) after reduced intensity conditioning as a consolidation treatment for elderly patients with AML in complete remission.

Methods
Patients with a matched sibling or with an unrelated donor, who have entered first remission (CR1), will be eligible for randomization in a 2 (SCT): 1 (nonSCT) fashion. Patients without a donor will receive post-remission therapy as scheduled at the local trial site.

Potential advantage for patients
Evaluation of the presently best available therapeutic option to treat elderly patients with AML in first remission.

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Schwenkglenks Matthias | **A health economic cost-utility analysis alongside the randomized controlled clinical trial SAKK 75/08: multimodal therapy with and without cetuximab in patients with locally advanced oesophageal carcinoma: an open-label phase III trial**
(KLS 02757-02-2011)
Duration: 01. 07. 2011–01. 07. 2014

Cetuximab is a monoclonal antibody used in cancer therapy. A clinical trial studies the effectiveness of this drug in patients with locally advanced oesophageal cancer. As cetuximab is an expensive drug, the question arises whether the achieved treatment effect justifies the additional costs. A health economic "piggy-back" study alongside the clin-

ical trial is conducted to answer this question. In addition to clinical parameters, all medical resources used by the patients are recorded, both during and after the end of the study treatment. These resources are subsequently converted into costs. Additional costs are compared with the gain in patient survival.

The resulting cost-effectiveness ratio provides information on whether cetuximab treatment of the patient group studied makes good use of scarce financial resources or whether these could be put to better use elsewhere in the health care system.

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Speiser Daniel E. | **Characterization of T-cell activation and suppression in melanoma patients by *ex vivo* analysis of myeloid, lymphoid and tumour cells**
(KFS 02836-08-2011)
Duration: 01.04.2012 – 31.03.2015

Tumour tissues have the unfortunate property of suppressing immune defence in cancer patients. Our project aims to identify the underlying mechanisms in patients with malignant melanoma. Several cell populations have been described to contribute to immune suppression: cancer cells, stroma cells and various bone marrow-derived cells. We will characterize these cells with novel technologies in cellular and molecular biology.

Our project should allow us to capture essential biomedical components of cancer simultaneously, such that we obtain a better overview of the dominant mechanisms causing malignant diseases. Interactions between cancer tissue and the immune system are also important for the susceptibility of the whole organism to develop metastases. Our data will allow improvement of cancer treatments for better strengthening of the patient's immune defence.

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Terracciano Luigi M. | **Dissecting the role of HOXA13 in hepatocarcinogenesis** (KFS 02867-08-2011)
Duration: 01.01.2012 – 31.12.2014

By comparing the HOX gene network expression, we recently identified the locus A as the part of the network most significantly involved in hepatocarcinogenesis. Inside the locus HOXA we identified the gene HOXA13 as the most deregulated in HCC.

This project is aimed to verify the role of HOX A13 in hepatocarcinogenesis at transcriptional and posttranscriptional level. We will perform transcriptome analysis of a large series of paired HCC/non-tumourous liver biopsies, comparing the transcriptome data with the fold of HOXA13 mRNA increase detected by real-time polymerase chain reaction (PCR). The same will be done with all the other genes potentially involved with the proposed molecular mechanism. The patterns identified will be connected with clinical pathological features of the patients. Crucial genes identified through transcriptome analysis will be validated at mRNA and protein level by real-time PCR, immunohistochemistry (IHC), and Western blot analyses to compare the expression between mRNA and protein.

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Vassella Erik | **Role of microRNAs in regulating EGFR signalling and cytotoxicity induced by receptor tyrosine kinase inhibitors in non-small cell lung cancer**
(KFS 02826-08-2011)
Duration: 01.02.2012 – 31.01.2015

Lung cancer is the primary cause of cancer-related cell death in humans. Since the discovery of new inhibitors of the epidermal growth factor receptor tyrosine kinase (EGFR), which led to increased survival, there is new hope for the treatment of lung cancer, but only few patients can profit from therapy.

The aim of this study is to investigate whether microRNAs are implicated in the development of resistance to EGFR inhibitors in lung cancer cells. These short regulatory RNA molecules play an important role in tumourigenesis. In a first part, we aim to identify microRNAs that are induced by the EGFR signalling and investigate the cellular processes in which these microRNAs are involved. In a second part, a microRNA library will be screened for microRNAs conferring resistance to EGFR inhibitors.

Those microRNAs that are involved in the EGFR signalling pathway may be interesting targets for an adjuvant therapy.

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Zucca Emanuele | **A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of mediastinal radiotherapy after rituximab-containing chemotherapy to patients with newly diagnosed primary mediastinal large B-cell lymphoma (PMLBCL)** (KFS 02859-08-2011)
Duration: 01.01.2012 – 31.12.2014

The PMLBCL is a kind of lymphoma that mainly affects young women. The prognosis is generally good, but an intensive initial treatment is required, because a salvage therapy for recurrence is more difficult than for other types of lymphoma. The correct initial treatment is therefore crucial. Moreover, there is a dilemma between the need to obtain a maximum percentage of healing with aggressive treatment and the need to reduce side effects. In this context, some studies have shown better results for patients who received radiotherapy after chemotherapy. Positron emission tomography (PET) is now available, and it could help to distinguish patients with residual active disease so that only these patients could receive radiotherapy.

Study objective
This study could help to individualize the treatment by using PET scans to identify patients with inadequate response to chemoimmunotherapy who could benefit from radiotherapy.

Method and procedures
Patients will be enrolled on the basis of the clinical and local pathologic characteristics of their lymphoma and preregistered before starting the chemotherapy programme, after giving their signed consent. Patients who have received one of the standard anthracycline-based chemotherapy regimens and at least six doses of Rituximab, and who have a FDG-PET/CT scan reported as negative after central review will be randomized to either no further treatment or consolidation with radiotherapy.

Potential benefits for patients
This study will eventually allow individualized treatment for each patient by adapting it to the PET response, limiting the indication for additional radiotherapy only to patients who show an inadequate response to chemoimmunotherapy.

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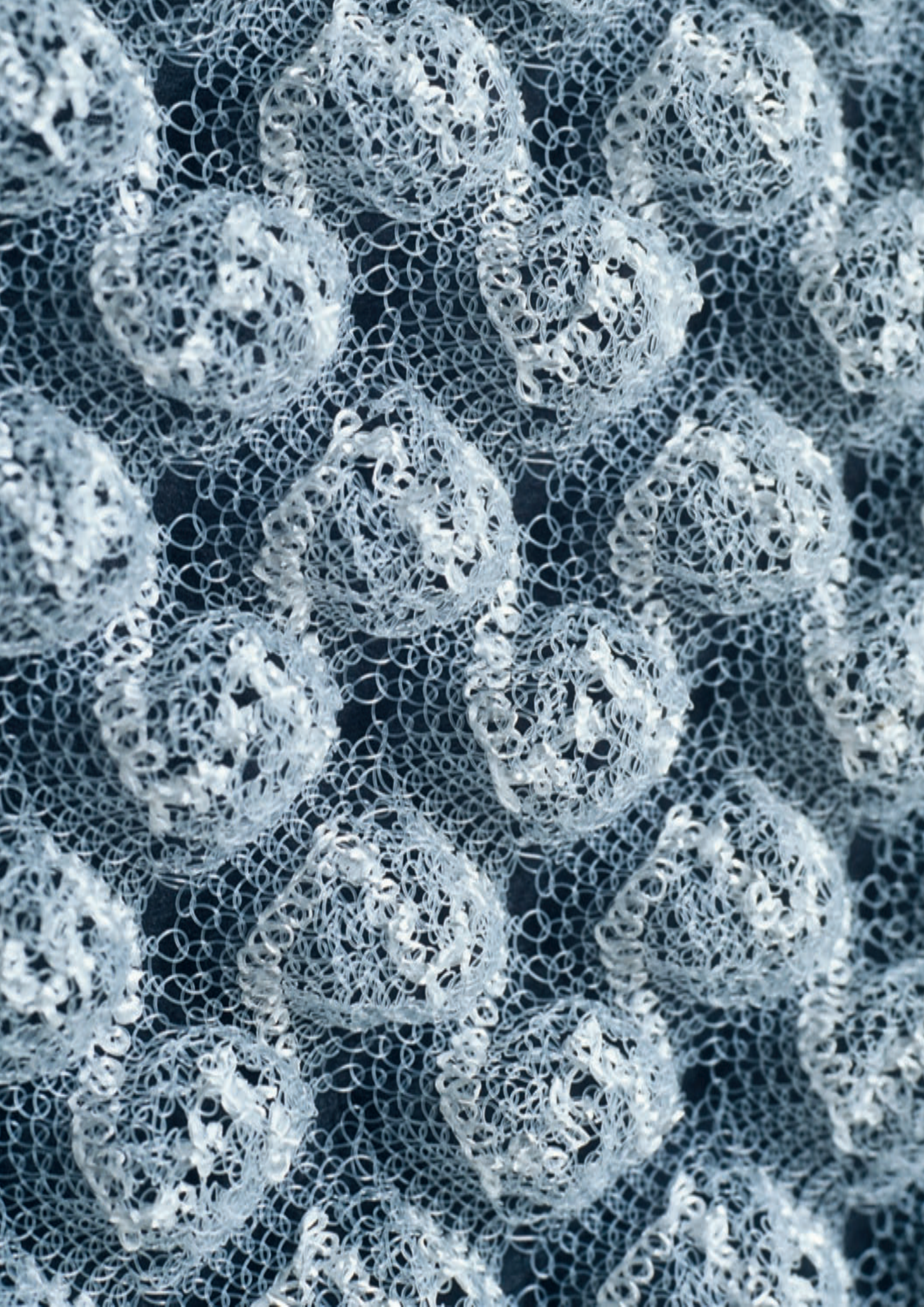

Psycho-oncology and families of persons with cancer

The psychological distress of family members of persons with cancer was not viewed as a serious problem until just a few years ago. Today we know, however, that psychological distress can be just as severe for family members as for the persons with cancer themselves. The extent of family members' distress depends among other things on the type of relationship with the person with cancer – such as whether the cancer patient is their spouse/partner, child, parent, or sibling.

Family members' psychological distress

Adult family members are often the most important persons providing care and support to persons with cancer. This mostly has serious consequences for their lives. They have frequent work absences, for instance, or they withdraw from social life. Even if family members are not primary caregivers, they can be strongly adversely affected by the illness. The strains and pressures take many forms: fear of losing the ill family member, existential threat to family life, exhaustion due to additional household responsibilities or child care, changes in spousal or family roles, confrontation with changes in the person with cancer, and insecurity in dealing with the topic of cancer. If the family has children, there are special issues and problems. If one parent is ill, parents have the tendency to protect their children from distress and often do not talk to them about the disease. However, children want to be informed and included. As they notice that something is not right but do not know what it is, their parents' silence makes them feel insecure. If a child gets cancer, the despair of the parents is great, and because their worry about the child takes centre-stage, they often pay insufficient attention to the needs of their other children.

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In studies, family members rate their distress at approximately the same level as the patients themselves. Thirty to fifty per cent of family members have clinically relevant psychosocial distress in the form of depression, anxiety disorder, or adjustment disorder. Psychological disorders are an important reason why family members of patients with cancer should definitely be included in a psycho-oncological screening and if necessary receive treatment as well. Family members are at risk of performing their role as a support person for the person with cancer to the point of exhaustion. They often do not dare to speak of their worries and distress. Precisely at times when it would be important for them to share with trusted persons, this speechlessness can lead to social isolation. Psychological disorders are not at all the only reason for psycho-oncological support for family members as well as patients. Exhaustion, isolation, personality changes in the person with cancer, family conflicts, unfavourable coping behaviours, and other things can also be reasons for the need for support.

Lack of psychosocial care for family members

In 2005 the Swiss Cancer League carried out an inventory of psychosocial services for cancer patients and their family members. The stocktaking revealed that every second family member (and every second patient) has a need for psychosocial support that is not met. Institutions and private providers of psychosocial support for cancer patients normally offer their services also to the families. However, the services available differ greatly across cantons and regions, and there are only few special services for family members of persons with cancer on offer. In contrast to the provision of medical care, the problem of inadequate provision of psycho-oncology services for families and patients is a general problem in oncology. For one thing, outpatient services are rarer than inpatient services. For another, psycho-oncology services are found much more rarely in basic care and in general hospitals than they are in specialized cancer centres or university hospitals.

According to the national health monitoring, there are treatment gaps in the area of mental health generally in Switzerland. With cancer, distress at the psychological level often does not fulfil the formal criteria for a psychological disorder. Psychological support for these persons thus serves primarily preventive purposes. In the area of prevention, too, the 2011 OECD report on the health care system in Switzerland confirmed that there is a general deficit. The conditions for psychological support in Switzerland are therefore basically poor. The National Cancer Programme (NCP) 2011–2015 seeks to counter this: The psychosocial care of persons affected directly and indirectly is to become an integral part of cancer care. The NCP 2011–2015 finds fault with the inadequate care and demands that specific offers of assistance for family members of persons with cancer be developed, especially for children of parents with cancer. The empirical bases for this are available.

Utilization of psycho-oncology services

The fact that a need exists does not tell us whether people actually utilize psycho-oncology services. Even in a situation of exceptional distress such as when someone in the family is diagnosed with cancer, many family members have a high threshold before seeking psychological services. The following factors are responsible for low utilization of the existing support services:

– Family members often push themselves to their limits and express their need for support only guardedly or not at all.

– As compared to patients' needs, family members' needs for information and support are often significantly less recognized and taken into consideration by medical personnel.
– Information on available psycho-oncology services is often not available, and even physicians and nurses are not informed.
– Oncological specialists focus on their biomedical core areas and for this reason pay little attention to psychosocial needs.
– Utilization of psychological support services is still today associated with a stigma (from the point of view of both people affected and healthcare professionals).

The threshold before seeking psycho-oncology services is lower, if psycho-oncology services are tightly integrated in the medical field. Studies show that the services are utilized more frequently when patients know the psycho-oncologist personally than when there are impersonal information brochures in the waiting room. Outreach to family members with psycho-oncology services must be integrated in the treatment and support process. Here the treating physicians and their communications with the people involved play an important role. Whether, and in what way, physicians address the psychological situation of their patients and patients' family members is likely to send an important message. Active and professional listening and speaking by the main treating physicians can be decisive in whether or not people utilize the needed support services.

Existing differences and gaps

In Germany, for example, persons with German as their first language have a more positive attitude towards psychotherapy than persons with Turkish as their first language. This fact is likely to be similar in Switzerland and for other groups with a migration background. For this reason, the undersupply of psychotherapy is likely to be greater among immigrants than among the population as a whole. Differences between the sexes have also been found: In general, more women than men utilize psychotherapy services. However, among persons with cancer, this is not always the case. Men do not fundamentally have better mental health. The reason probably has more to do with a higher inhibition level before seeking psychotherapy services.

There exist great deficits in psycho-oncology services for persons affected by cancer in assessment of distress and need, in information provision about available support services, and in financing the services. To close these gaps, measures such as the following are useful:

– Systematic assessment of distress and need (psychosocial screening), also for family members, starting at diagnosis and repeatedly up to the patient's rehabilitation or some months after the patient's death
– Raising the level of awareness/information of primary treating physicians about psychosocial support services
– Expansion and differentiation of care services (triage): Differentiation between psycho-oncology services and psychotherapy
– Standard national regulation of paying the costs through the basic health insurance
– Promotion of psycho-oncology health services research.

Problems and focuses of psycho-oncology research

Not enough funding is going into psycho-oncology research in Switzerland, especially when it comes to psycho-oncology research with family members. Grants from the Swiss National Science Foundation are conditional upon strict scientific research designs that are hard to implement in the area of psycho-oncology. And of the funding by the Cancer Research Switzerland foundation and the Swiss Cancer League only approximately five per cent is granted to research projects on psychosocial topics.

Further problems are encountered during implementation of psychosocial research. To include patients and their family members as early as possible in a study, researchers are dependent upon first care physicians and their willingness to cooperate. Here there are great differences in the extent of physicians' understanding for the psychological and social level in patients with cancer and the situation of their family members. Physicians therefore vary in their willingness to obtain participants for a psychosocial study of persons directly and indirectly affected by cancer. Patients and their family members do not share this reserve, as the high response rates for psycho-oncology surveys have shown. Their willingness to participate in a study is not dependent upon the severity of the illness. And their comments when asked if they experienced any strain or any relief when filling out an hour-long questionnaire are remarkable: Two-thirds of the participants found the task "neither a strain nor a relief". Some participants even felt a sense of unburdening after filling out the survey.

Psycho-oncology research deals with the bio-psycho-social interplay of the development, treatment, and progression of cancer and includes family members. The focus today is on the following research topics:

- Epidemiology of mental disorders secondary to cancer, in patients and family members
- Coping – as an individual, as a couple, as a family
- Psychological interventions for individuals, couples, families (siblings, parents, children), and groups

Applying research findings in practice

The findings of psycho-oncology research serve practice in many ways. As distress in spouses/partners can be just as high as, and in many cases higher than, patients' distress, they also need support. Here merely prescribing medications has been found to be not very effective. Combined psychological and pharmaceutical treatments are more effective. The most important resource for both partners in a couple is usually a good relationship. Not communicating with each other so as not to burden the other with one's own worries is a well-meant but in the end counterproductive behaviour. It leads to inner withdrawal and to distance between the partners. For this reason, helping people deal with cancer together is an important intervention.

There are also obstacles to implementing psycho-oncology research findings in the world of practice. For instance, despite their high level of distress, spouses/partners of persons with cancer are not very willing to seek support services. One possible reason for this is the often dissatisfactory rulings on payment of the costs. A national law concerning payment for the services could bring us a step closer to the comprehensive cancer care that has been de-

manded. Clinical economic analyses have shown that psycho-oncology interventions are often worthwhile also financially. The central point, as mentioned above, is that patients with cancer and their family members should be informed – early on and independently of the stage of the disease – about available psycho-oncology support. This recommendation, too, is based on empirical evidence.

Alfred Künzler, PhD

Alfred Künzler has a doctorate as specialist psychologist (*Fachpsychologe FSP*) for psychotherapy and for health psychology awarded by the Federation of Swiss Psychologists. Up to 2011 he worked as a clinical psycho-oncologist at the Centre of Oncology/Hematology at Aarau Cantonal Hospital, at first contracted by the Aargau Cancer League and then by Psychiatric Services Aargau. In cooperation with the University of Bern and University of Zurich he conducted diverse psycho-oncology research studies that were supported by the Aargau Cancer League, the Swiss Cancer League, Oncosuisse, and the *Stiftung zur Krebsbekämpfung*. Since the start of 2012 Künzler has been the director of the Coordination Office of the new Network Mental Health Switzerland, a joint project of the Swiss federal government, the cantons, and Health Promotion Switzerland.

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Diana Zwahlen studied psychology at the University of Bern and completed training in psychotherapy with a focus on systemic therapy. She has a doctorate as psychologist (*Psychologin FSP*) of the Federation of Swiss Psychologists. Her doctoral research was conducted in cooperation with University Hospital Zurich; the title of her dissertation, which was supported by a scholarship from the Zurich Cancer League, was “Families Facing Cancer”. After a research stay in Boston, Massachusetts (USA), she returned to Switzerland, where she is currently working as a psycho-oncologist at the Department of Medical Oncology at Bern University Hospital and at the University Hospital Basel. She is a member of the board of Swiss Society of Psycho-Oncology (SGPO).

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Psychosocial research

List of completed research projects in 2011

Despland Jean-Nicolas | OCS 02338-02-2009 | CHF 251,350.–
Institut universitaire de psychothérapie (IUP), Centre hospitalier universitaire vaudois (CHUV), Prilly
Communication in cancer care: the relationship between clinician's defense mechanisms, patient satisfaction and information recall

Rehmann-Sutter Christoph | OCS 01960-10-2006 | CHF 264,840.–
Institut für Medizingeschichte und Wissenschaftsforschung der Universität zu Lübeck, Lübeck, Deutschland
Terminally ill patients' wish to die: the attitudes and concerns of patients with incurable cancer about the end of life and dying

Stiefel Friedrich | KLS 02353-02-2009 | CHF 124,200.–
Service de psychiatrie de liaison (PLI), Centre hospitalier universitaire vaudois (CHUV), Lausanne
Effects of communication skills training on oncology clinicians' defense mechanisms, communication outcomes and working alliance – extension

Presentation of completed research projects in 2011

Despland Jean-Nicolas | **Communication in cancer care: the relationship between clinician's defense mechanisms, patient satisfaction and information recall** (OCS 02338-02-2009)

Communication has become a key element in oncology and has important consequences for both the patient's and the clinician's well-being. Clinicians often need to regulate their emotions that arise during the discussion of sensitive topics, such as limited life expectancy. The different ways of emotion regulation might influence the quality of communication between the clinician and the patient.

Aim
We wish to better understand how the clinicians' emotional regulation might influence communication in oncology.

Method
We analyse discussions between patients and their clinicians in several hospitals in French-speaking Switzerland. We especially pay attention to the clinicians' defense mechanisms used to react to the emotional content of the discussions and to their relation to the clinicians' stress level and the patients' satisfaction with the communication.

Results
Over 100 patients and 15 clinicians have already agreed to participate in our study. First results show that most patients are highly satisfied with their relationship with their clinician. Preliminary analyses confirm our hypothesis, which states that patient satisfaction is influenced by the stress level of the clinicians during the discussions. The defense mechanisms of the clinicians further explain the relationship between the stress level of the clinicians and patient satisfaction. This would mean that the way that clinicians defend themselves against difficult emotions during stressful discussions has an influence on the quality of the communication perceived by patients.

Potential advantages for the patients
A better understanding of the influence of the clinicians' emotional regulation on communication in oncology will allow improvement of patient-clinician communication and thus of patient and clinician well-being.

This project is not yet completed and has been extended until 2014 (KFS 02828-08-2011).

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Rehmann-Sutter Christoph | **Terminally ill patients' wish to die: the attitudes and concerns of patients with incurable cancer about the end of life and dying** (OCS 01960-10-2006)

On the basis of 30 case studies with terminally ill oncology patients (116 qualitative interviews with patients, caregivers and relatives) in three different palliative settings in Switzerland, this project analysed the moral understandings, the intentional, interactive and semantic details in statements about wishes to die and wishes to live. Patients had already been informed about the incurability of their disease; they consented to participate, and their main physician agreed to their enrolment in the study. Data analysis and interpretation followed phenomenological and hermeneutical methodology, based on Grounded Theory and Interpretive Phenomenological Analysis.

The study found that a wish to die is not a simple state of mind but a complex, dynamic and social space of agency and meaning making that cannot be scaled quantitatively. Ideal typically, nine types of intentions could be mapped and distinguished from a wish to live and the attitude of acceptance of dying. Many wish-to-die statements did not imply a wish to hasten death. A wish to hasten death appeared as a special case of a wish to die. Other types of wishes to die (without hastening) include looking forward to dying, hoping that dying proceeds faster, and desiring to die. Wishes to hasten death include hypothetically considering hastening death if the situation becomes unbearable and considering hastening death but still excluding it for moral reasons, or considering it as a realistic option. The strongest inclination towards death is an action-related will, which can be a request, a refusal or the will to take an active measure.

The contents of a wish to die were analysed regarding the subjective reasons, meanings and functions of the wish. Ten different groups of meanings appeared within this sample, ranging from the hope that death brings an end to long suffering, the hope that death will unburden others from oneself, to the hope that a good life is completed in its proper ending.

The data provide insight into patients' own complex, often ambivalent processes of meaning making at the end of life. Patients constitute themselves as ethical agents within their social relationships. Interdependence, voluntary or non-voluntary responsibilities and obligations, assumed or real moral understandings or reactions of others, sociocultural practices and legislation shape a patient's wish to die. The performative aspect of wish to die statements seems to be particularly relevant: A wish

adopts significance for certain others, as soon as it is stated to them. It is always told to somebody and changes something in this relationship. A wish to die is to be seen as a relational space of moral interactions.

Future bioethics, palliative care research and practice should recognize the constitutive factors, the mental, social and moral structure of wish to die statements. A conception of relational autonomy might best be suited to address this and will help us to recognize patients' wishes.

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Stiefel Friedrich | **Effects of communication skills training on oncology clinicians' defense mechanisms, communication outcomes, and working alliance – extension** (KFS 02715-08-2010, prolongation of the project KLS 02353-02-2009)

Since 1999, the Swiss Cancer League has organized communication skills training (CST) for the medical oncologists and the nurses working in oncology based on videotaped interviews with simulated patients, case discussions, and role-playing exercises. The training is completed by individual supervision of participants during a six-month period, followed by a second videotaped interview with a simulated patient. It has been demonstrated that clinicians participating in CST significantly improve different aspects of communication, such as an increase in patient speaking time, use of open questions, investigation of patient concerns, and empathic response. Little is known, however, about the underlying mechanisms of this improvement.

In the first part of the project, we showed that not all clinicians benefit equally from CST. Clinicians who used defense mechanisms – broadly defined as emotional regulatory processes – that are more adaptive were the only clinicians who improved their communication skills. The current extension of the study, started in September 2009, aims to investigate the relational aspects of communication – the therapeutic or working alliance – which is the more robust predictor of psychotherapy outcome but also of any professional relationship with patients. The project will contribute to better understand the underlying mechanisms of how CST have a positive or a negative effect on communication and the relationship; the results may lead to a deeper insights into the way CST work and identify new markers of communicational improvement.

Transcribed videos of 57 participants (75.4% women; 52.6% medical oncologists) in the French-speaking CST were compared to a control group of 56 clinicians (62.5% women; 37.5% medical oncologists) who did not have CST training and who conducted two videotaped interviews – with a six months' interval – with the same simulated patients and the same scenarios used in CST. Measurements consisted of widely used and validated measures such as the Defense Mechanism Rating Scales (DMRS), adapted for the coding of the clinician's defenses, the Working Alliance Inventory – Short Form Revised (WAI-SR), and the Roter Interaction Analysis System (RIAS).

Whereas the working alliance did not improve under CST, the quality of verbal communication was related to alliance. Positive talk (agreement, approval, laughter, or jokes) and psychosocial counseling were related to higher alliance, whereas negative talk (criticism or disagreement) and biomedical information were related to weaker alliance. Finally, the defensive functioning of the clinician was also related to the working alliance, more adaptive defensive functioning being related to higher alliance.

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List of approved research projects in 2011

Total funds allocated: CHF 931,300.–

Ballmer Peter E. | KFS 02833-08-2011 | CHF 245,500.–
Klinik für Innere Medizin, Departement Medizin, Kantonsspital Winterthur, Winterthur
Influence of a combined intervention by nutritional support and physical exercise on quality of life in cancer out-patients treated in palliative intention

Berney Alexandre | KFS 02776-02-2011 | CHF 164,000.–
Service de psychiatrie de liaison (PLI), Centre hospitalier universitaire vaudois (CHUV), Lausanne
Pregraduate training for medical students on breaking bad news in oncology

Burton-Jeangros Claudine | KFS 02816-08-2011 | CHF 80,800.–
Département de sociologie, Université de Genève, Genève
Women's views on cervical cancer screening. A qualitative study of barriers to screening and HPV self-sampling acceptability

Despland Jean-Nicolas | KFS 02828-08-2011 | CHF 185,900.–
Institut universitaire de psychothérapie (IUP), Centre hospitalier universitaire vaudois (CHUV), Prilly
Communication in cancer care: the relationship between clinicians' defense mechanisms, patient satisfaction and information recall

Continuation of the project:
Despland Jean-Nicolas | OCS 02338-02-2009 | CHF 251,350.–
Institut universitaire de psychothérapie (IUP), Centre hospitalier universitaire vaudois (CHUV), Prilly
Communication in cancer care: the relationship between clinician's defense mechanisms, patient satisfaction and information recall

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?

Continuation of the project:
Lehr Hans-Anton | OCS 02209-02-2008 | CHF 204,400.–
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?

Strasser Florian | KLS 02785-02-2011 | CHF 176,100.–
Onkologische Palliativmedizin, Departement Innere Medizin und Palliativzentrum, Kantonsspital St. Gallen, St. Gallen
Decision criteria guiding chemotherapy in palliative intention: prospective study comparing patients', doctors' and nurses' responses

Presentation of approved research projects in 2011

Ballmer Peter E. | **Influence of a combined intervention by nutritional support and physical exercise on quality of life in cancer out-patients treated in palliative intention** (KFS 02833-08-2011)
Duration: 02. 01. 2012 – 01. 01. 2015

Loss of appetite and fatigue are highly prevalent among cancer patients. Subsequently, cancer patients often experience weight loss and muscle wasting during the course of their disease. These symptoms are strongly associated with an impaired quality of life and a reduced tolerance and response to anti-cancer therapy.

Preliminary evidence suggests that a multimodal approach combining dietary interventions with physical exercise is able to prevent the occurrence of these symptoms. In this study, we will examine the effect of nutritional support and regular physical exercise on the quality of life of cancer patients in a prospective randomized trial.

Patients will be individually counselled by a professional dietician and will participate regularly in a physical exercise programme led by a professional physiotherapist. The strong hope is that this will improve the quality of life, the physical and nutritional status, and the course of the disease in patients suffering from cancer.

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Berney Alexandre | **Pregraduate training for medical students on breaking bad news in oncology**
(KFS 02776-02-2011)
Duration: 01. 08. 2011 – 01. 08. 2013

Breaking bad news (BBN) occurs in daily clinical practice, especially in oncology, and has a significant impact on both patients and physicians. Most physicians report a lack of confidence in performing the duty of BBN and did not receive formal training in BBN. Pregraduate training in BBN that is focused on complex medical information processing in difficult emotional situations may improve future physicians' skills. In our study, we will give medical students the opportunity to conduct videotaped interviews with a simulated patient (SP) in a BBN task using an oncological scenario and to benefit from individual supervision by a faculty member. If it is proved efficient, this practical training will be implemented in the curriculum of our medical school with the hope that this will contribute to better care for oncological patients.

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Burton-Jeangros Claudine | **Women's views on cervical cancer screening. A qualitative study of barriers to screening and HPV self-sampling acceptability**
(KFS 02816-08-2011)
Duration: 01. 02. 2012 – 31. 01. 2013

It is estimated that in Switzerland 30 – 40 % of women do not participate in cervical cancer screening. Social sciences studies identified several obstacles, including barriers related to information, emotional barriers (embarrassment, discomfort), and practical barriers (access, interactions with professionals). It is expected that HPV self-sampling procedures could reduce some of these barriers. This study aims to describe women's views on cervical cancer screening, assess the different obstacles that restrict participation in screening, and evaluate the benefits and disadvantages of HPV self-sampling. Results will be based on 20 focus groups – representing 100 to 120 women – conducted in Geneva. The results will aid formulation of some recommendations regarding the organization of screening.

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Despland Jean-Nicolas | **Communication in cancer care: the relationship between clinician's defense mechanisms, patient satisfaction and information recall** (KFS 02828-08-2011)

This project is the continuation of the project OCS 02338-02-2009, see page 122 for intermediate results. The final results are expected for 2014.

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Lehr Hans-Anton | **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?** (KFS 02775-02-2011)
Duration: 01.10.2011–01.04.2012

In the face of the growth in biobanks, a balance must be found regarding patients' rights and the requirements of biomedical research. Ethical principles dictate that the general public should participate in decisions regarding legislation and guidelines on the use of human tissue, but little is known about public opinion on these issues. This study examines perceptions obtained from a representative sample of 1,601 Swiss residents. Computer-assisted telephone interviews were conducted in 2010. The questionnaire was informed by a previously-conducted qualitative study. The topics covered included awareness and attitudes regarding use of human tissue for research and informed consent. Only a third of the participants questioned had given any previous thought to the use made of excised tissue samples.

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Strasser Florian | **Decision criteria guiding chemotherapy in palliative intention: prospective study comparing patients', doctors' and nurses' responses** (KLS 02785-02-2011)
Duration: 01.08.2012–01.02.2015

In patients with advanced, incurable, symptomatic cancer the two criteria tumour control and toxicity are considered as insufficient to alone guide individual decisions for chemotherapy in palliative intention (CPI). The additional criteria symptom control and physical function are often used, conceptualized for some tumours as patient-centred clinical benefit criteria. However, clinical trials investigating these criteria as primary endpoints are rare, the validity of clinical trials having Best Supportive Care control arms to inform decisions is weak, and extrapolation from tumour response to symptom benefit is often unreliable. Further individual and contextual criteria may influence decision processes for CPI, such as the patient's (remaining) life goals, symptom control before CPI, logistic factors (e.g., time schedule, access to clinic), or costs. In addition to the criteria for CPI itself, there are other known significant factors that influence health care decisions (F-HCD) in general, such as age, family status, culture, life expectancy, or decision-making preferences. There is a lack of available, context-relevant and measurable decision criteria for CPI.

Aims

1. To systematically identify CPI-decision criteria considered to be important by experienced, communication competent physicians, patients, and nurses when considering CPI in a multidisciplinary, integrated oncology and palliative care setting or a primary care physician (GP) office experienced with advanced cancer patients setting.
2. To investigate the use of CPI decision criteria in cancer clinics and GP offices when considering CPI.

Methods

First, the literature will be reviewed systematically (SLR) to investigate current evidence of decision criteria in advanced cancer care. As second step, physicians (oncologists and GPs), patients, and nurses, recruited upon inclusion criteria, participate in a formal Delphi process (focus groups) to collect potential factors (considering also results of the SLR, narrowed down by the study team including international experts) and decide through voting to make the decision criteria set for CPI. As the third step, in a prospective, multicentre study, immediately after a decision has been made in a physician-patient visit regarding a CPI, physicians and patients independently complete the decision criteria set for CPI (yes/no) and quantify the importance of each decision criteria. Agreement between patients and physicians for presence and separately for importance of decision criteria are summarized using the kappa statistic.

Potential significance of the project

A novel set of decision criteria for CPI may serve quality initiatives, education, and clinical trial design.

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Cancer registration and cancer epidemiology: An inseparable pair

The relationship of cancer registration and cancer epidemiology is that of an undividable pair: The value of one is connected to the other. Technically, cancer registration could be done without including other areas of cancer epidemiology, and cancer epidemiology has many areas not dependent on cancer registration. But both cancer registration and cancer epidemiology are fundamental components for maintaining an effective public health programme against cancer. For countries like Switzerland with long life expectancies, cancer (a disease of aging) is a serious public health problem. Because cancer is a major cause of morbidity and mortality, most countries have public health programmes, informed by cancer registration, to minimize its impact on society.

Cancer registration for cancer monitoring

Population-based cancer registration is the process of documenting all cancer diagnoses within a specified population (e.g., community, region, or country). Cancer registration is the only way to accurately understand how many people in a population are getting and living with cancer and what types of cancer they get and have. It is also instrumental to the fight against cancer. Cancer registration is common worldwide. Currently, there are 184 countries included in GLOBOCAN 2008, the International Agency for Research on Cancer (IARC) database [1, 2]. The IARC is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer and the mechanisms of carcinogenesis and to develop scientific strategies for cancer prevention and control.

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A primary goal of population-based cancer registration is to provide information on the burden of cancer within a population – also known as cancer monitoring. By international standards, cancer monitoring includes four disease measures: incidence, mortality, prevalence, and survival. In practice, quantifying cancer burden is a complex task (i.e., many factors related to cancer), and no single measure or set of collected variables encompasses all aspects. Thus, cancer monitoring is best done using all four measures within a broader context of cancer epidemiology [3].

Limitations in Swiss cancer registration

In Switzerland, we have cancer registration in some but not all cantons, with varying timeframes and information being collected. Swiss cancer registration programmes began over 40 years ago and have evolved slowly, expanding over time. Today, most cantons participate in either an existing cancer registry or are creating a cantonal or regional population-based registry. Data from these programmes allows us to annually estimate but not calculate the actual national burden of cancer restricted to measures of incidence and mortality. Ironically, the only publically available estimates of national cancer prevalence and survival have been provided by international studies [4–8].

Limitations in Swiss cancer monitoring are due to less than full population coverage, limited participation of some registries in the national programme, and insufficient national follow-up. To properly understand and effectively influence the burden of cancer in Switzerland a national cancer registration programme needs to achieve complete national coverage that allows regular assessment (not estimation) of all four (not only two) measures of national disease burden: incidence, mortality, prevalence, and survival. It is also imperative that the information collected through a national Swiss cancer registration programme be sufficient to promote other important areas of cancer epidemiology.

Cancer registration for cancer control planning and evaluation

Cancer epidemiology in its most basic broad terms is the study of factors associated with cancer. Over the years and in many countries, cancer registration data has played a significant role in furthering cancer epidemiology. The information collected from cancer registration forms a basis for several areas of epidemiologic interest: cancer reporting, cancer control, and cancer-related research. Collecting population-based cancer data requires a considerable investment from both persons with cancer and societies providing the necessary funds. Consequently, the data collected should be used for the maximum benefit of those contributing. The IARC advises "the collection of information on cancer cases and the production of cancer statistics are only justified, however, if use is made of the data collected. Cancer registry information may be used in a multitude of areas, and the value of the data increases if comparability over time is maintained" [3]. Thus, whenever possible cancer registration data should be used to its fullest potential for research, public policy, patients, and the general public.

Cancer reporting is a primary use of cancer registration data and directly informs cancer control efforts. Understanding the current burden of cancer helps set priorities for allocating health resources. Analysing the data by cancer site, sociodemographic characteristics, treatment modality, and other important factors guides planning and evaluation of cancer control programmes (i.e., determine whether prevention, screening, and treatment efforts are making a difference, identify health disparities, etc.). Using the information collected from cancer registration is an efficient way to plan and evaluate all aspects of cancer control. Of course, the accuracy of the data plays a major role in the usefulness of the information. Cancer control planning based on the most current and accurate cancer information can respond more effectively to the specific cancer needs of a society. This can be done by implementing policies and encouraging research customized to preventing cancer, detecting it early, curing it, and caring for those affected by it within the monitored population.

Research topics in cancer epidemiology

Cancer registration data used for research purposes provides equal benefit to the individual and society. Much of what we know today about causes of cancer began with descriptive and etiological epidemiological research. Even a cursory investigation shows the impact of cancer registration on cancer epidemiology research. A PubMed (online library for peer-reviewed publications) search of the terms "cancer registry" and "cancer registration" resulted in over 30,000 peer-reviewed articles in a wide range of cancer-related topics. Epidemiological research, based on cancer registration, is a valid and efficient way to advance clinical, epidemiologic, and health services research as well as to inform the process of translating research to practice and policy. Preventing cancer requires knowledge on risk factors. How lifestyle, genes, and environment interact to cause cancer is a major challenge to which cancer epidemiology studies can contribute. The quality of cancer care received can also be evaluated. Patterns of care studies, linkage studies with clinical and special population cohorts, biological samples, health utilization data, and environmental and exposure data allow critical questions in cancer epidemiology to be asked and answered.

The IARC's recommendation to make good use of cancer registration data implies access to data of usable quality [3]. The value of cancer registration depends on the quality of data and the extent to which the data are used. In Switzerland we are just starting to develop a national quality assurance programme and hope in the near future to provide online access as well as public use datasets like other countries with more developed national programmes. Increasing access and overcoming challenges to a national cancer registration programme will further promote cancer epidemiology in Switzerland. Promoting cancer epidemiology will encourage many scientific contributions, ranging from etiological research, to primary and secondary prevention, to healthcare planning and quality of patient care.

Swiss federalism and challenges

As mentioned, Switzerland has several challenges that need to be addressed before the necessary pair of cancer registration and cancer epidemiology provides an infrastructure robust enough to inform and propel nationally focused advances in cancer like other international examples. There is a common adage that these challenges on the national level are the result of Swiss federalism.

As a foreigner dedicated to improving both cancer registration and cancer epidemiology in Switzerland, I believe comparisons with my homeland, the United States, another strong federalist society, are of interest. In the United States, cancer registration and cancer epidemiology have a long productive tradition spanning many decades. The United States (and Canada), like Switzerland, has a "bottom up" system of cancer registration, where cancer information is collected at the state level and contributed to a national programme. All 50 US states have state-based cancer registries and the federal government supports the Surveillance Epidemiology and Ends Results (SEER) programme (a nationally representative public use database). Both cancer registration and cancer epidemiology in the United States are cornerstones of cancer control, research, public policy, patient information, and regular public reports on cancer. There are over 7,000 cancer-related publications by SEER-related staff alone and over 4,000 peer-reviewed publications by keyword search "SEER" in PubMed [9]. Therefore, by comparison, I do not believe that the challenges we face here in Switzerland result from federalism or that federalism should inhibit our progress. On the contrary, I am optimistic that Switzerland will similarly and quickly follow the example of other countries to become a world leader in the fight against cancer. After all, Switzerland is an international leader in so many other areas, why not also in cancer registration and cancer epidemiology?

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After completing a Bachelor of Science in electrical engineering in 1985, Kerri Clough-Gorr worked for roughly 15 years as an engineer and technical business manager in industry before moving into the area of health care. She completed a Master of Public Health in 2000 and a Doctor of Science in Epidemiology in 2006, both at Boston University School of Public Health in the United States. Since 2009, she has been a senior research fellow in the International Health and Environmental Health Division at the Institute of Social and Preventive Medicine (ISPM) at the University of Bern. She has been the scientific director of the National Institute for Cancer Epidemiology and Registration (NICER) at the ISPM at the University of Zurich since 2010. Her research interests include cancer epidemiology and issues in geriatric assessment, with a special focus on the cancer experience of older adults.
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List of completed research projects in 2011

Egger Matthias | OCS 02288-08-2008 | CHF 169,300.–
Institut für Sozial- und Präventivmedizin, Universität Bern, Bern
Cancer epidemiology in older adults: population-based research of trends and factors associated with cancer mortality in Switzerland, 1990–2007

Kuehni Claudia E. | KLS 02224-03-2008 | CHF 410,000.–
Bereich Internationale Gesundheit und Umwelt, Institut für Sozial- und Präventivmedizin, Universität Bern, Bern
Childhood cancer and nuclear power plants in Switzerland: a census-based cohort study

Thürlimann Beat | KFS 02474-08-2009 | CHF 25,900.–
Brustzentrum, Kantonsspital St. Gallen, St. Gallen
Management of breast cancer in the elderly in Switzerland

Presentation of completed research projects in 2011

Egger Matthias | **Cancer epidemiology in older adults: population-based research of trends and factors associated with cancer mortality in Switzerland, 1990–2007** (OCS 02288-08-2008)

Objective

Cancer is a disease of aging that disproportionately affects older adults and often results in considerable public health consequences. The results from this funded project provide a comprehensive scientific representation of the impact of cancer on the fastest growing and most afflicted segment of the Swiss population.

Methods

We used the Swiss National Cohort (SNC) to answer critical questions related to the burden of cancer mortality in the population of Swiss older adults. The SNC is a national longitudinal data platform based on linking the 1990 and 2000 census data to mortality records (currently up to 2008, updated regularly). We included all SNC persons ≥65 years old (N=2,253,378) and cancer deaths 1991 through 2008 (N=208,239). Three census questionnaires covered the individual (marital status, educational level, profession, etc.), the household (household type, owned or rented accommodation, rent per month, etc.), and the characteristics of the housing (location, type of building, number of flats, age of building, etc.). Because the SNC is based on federally mandated census data and linked to all-inclusive federal mortality data, we were able to characterize age group-specific cancer mortality trends over a long period of follow-up and identify personal sociodemographic characteristics associated with cancer mortality in older adults nationwide. Total at risk person-time by older age-groups (65–74, 75–84, 85+ years respectively) in person years (PY) was 4,747,989 PY; 2,640,244 PY; 715,836 PY for men and 5,826,815 PY; 4,211,652 PY; 1,769,929 PY for women.

Results

Cancer mortality, except for lung cancer, increased with advancing age. Older men in all age groups had overall higher cancer mortality rates than older women and showed a consistent decline in all-cancer mortality. In contrast, older women in all age groups showed early declines with a levelling-off of all-cancer mortality beginning in 2000. For older men there appeared to be an education effect for all-cancer and lung cancer mortality; the highest rates were found in older men with compulsory education. Younger old women living alone or in peri-urban areas had the most sharply increasing lung cancer mortality rates.

The risk profile of dying from cancer was similar in older men and women across most sociodemographic characteristics: higher cancer mortality risk with lower educational attainment (all-cancer men HR=0.84 [95% CI 0.82, 0.85] tertiary, HR=1.09 [95% CI 1.07, 1.10] ≤compulsory, women all-cancer HR=0.95 [95% CI 0.92, 0.98] tertiary, HR=1.03 [95% CI 1.02, 1.05] ≤compulsory) and unmarried marital status. Cancer mortality risk factors varied less than hypothesized across older age groups. However, for outcomes and characteristics with age-specific variation, the oldest group (85+ years) generally showed lower cancer mortality relative risk (except for non-Swiss lung cancer risk).

Impact

This comprehensive epidemiological evaluation provides additional needed information about the aging-cancer nexus in developed countries. These results can help us to identify which groups of Swiss older adults are at greatest risk for cancer mortality. This information can be useful for cancer control programmes. Specifically, when used for targeting interventions, healthcare resources, and tracking cancer disparities over time. However, additional and continually updated epidemiological exploration of these factors is needed. Future investigations should include associations with cancer burden and their influence on the growing aging population in Switzerland and other developed countries.

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Kuehni Claudia E. | **Childhood cancer and nuclear power plants in Switzerland: a census-based cohort study (CANUPIS)** (KLS 02224-03-2008)

A 2007 study in Germany found an increased risk of cancer, particularly leukaemia, in children living near nuclear power plants (NPPs). These results led to concerns in Switzerland. Switzerland has five NPPs in four different locations. Around 1% of the Swiss population lives within 5 km, around 10% within 15 km of an NPP.

The CANUPIS study investigated this topic in Switzerland. We wanted to know if children who live near an NPP have an increased risk of cancer. We were particularly interested in leukaemia (blood cancer) developing in young children before the age of five years, as this group was most strongly affected in Germany. The project was funded by the Swiss Cancer League and the Federal Office of Public Health.

A subtle study design allowed us to minimize or avoid weaknesses of earlier studies in other countries. First, we did not only compare selected "cases" and "controls" but included in the study all children living in Switzerland. This was possible by including information on all children diagnosed with cancer from the Swiss Childhood Cancer Registry. Information on place of residence for all children in Switzerland (including healthy ones) came from the Swiss National Cohort, an anonymous dataset of the entire population of Switzerland. Second, we examined not only residence at the time of cancer diagnosis but also residence at birth, which reflects exposure during the vulnerable phase of prenatal and early postnatal development. Most childhood cancers are in fact caused by factors acting very early in life. Third, our analysis adjusted also for confounding factors: exposures that are more common in the vicinity of NPPs and might cause cancer themselves, such as electric power lines.

The study included nearly all children born in Switzerland between 1985 and 2009, more than 1.3 million children aged 0 to 15 years. Together, this resulted in an observation time of over 21 million person-years. For analysis, we divided Switzerland into four zones, by distance from NPPs: (I) regions lying between 0 and 5 km from an NPP, (II) regions in the distance of 5 to 10 km, (III) regions in the distance of 10 to 15 km, and (IV) the rest of Switzerland. We then compared the number of children diagnosed with cancer in regions I, II and III, compared to the number we would have expected based on the cancer risk in zone IV. This was done for all cancers diagnosed in children aged 0 to 15 years, all cancers diagnosed in 0- to 4-year-olds, and separately for leukaemias in 0- to 15-year-olds and 0- to 4-year-olds.

The results of the study were reassuring. In none of the age groups did we find a significantly increased risk of leukaemia or of all childhood cancers in children living near an NPP, neither for residence at birth nor for residence at the time of diagnosis. The confounders that we analysed had no relevant effect in this study. Because of the relatively small number of diagnosed cancers, there remains a certain statistical uncertainty. The study could therefore not totally rule out very small increases or decreases in risk. However, a result as in Germany, i.e. a more than twofold increase in risk, is highly unlikely for Switzerland.

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Thürlimann Beat | **Management of breast cancer in the elderly in Switzerland** (KFS 02474-08-2009)

Breast cancer (BC) is common in women aged 65 years old and older, a segment of the Swiss population that is growing rapidly. According to the projections established by the Swiss Federal Statistical Office, life expectancy at birth of females will continue to increase from 83.7 years in 2004 to 89.5 years in 2050 in the middle series scenario (to 91.5 years in the high series scenario, to 87.5 in the low series scenario). Accordingly, life expectancy at age 65 will increase from 21.5 years in 2004 to 25.5 years in 2050 (27 years to 24 years respectively). There is therefore an urgent need to better understand the influence of age on the early detection, diagnosis, and treatment of breast cancer and evaluate potential causative factors for the decrease in breast cancer-specific survival in the elderly.

Patients and methods

We included all or representative samples of patients with newly diagnosed breast cancer cases from seven Swiss cancer registries diagnosed between 2003 and 2005. Surgical and non-surgical breast cancer treatment was analysed over five age groups (<65, 65 to <70, 70 to <75, 75 to <80, and ≥80 years), and the predictive impact of patient age on specific treatments was calculated using multivariate logistic regression analysis.

Results

The proportion of locally advanced, metastatic, and incompletely staged BC increased with age. The odds ratio for performing breast-conserving surgery in Stage I–II (0.37), sentinel lymph node dissection in patients with no palpable adenopathy (0.58), radiotherapy after breast conserving surgery (0.04), and adjuvant endocrine treatment (0.23) were all in disfavour of patients ≥80 years of age compared to their younger peers. Only 36 % of patients aged 80 years or older with no palpable adenopathy underwent sentinel lymph node dissection, even though this technique is specially recommended in older women in order to avoid morbidity related to conventional axillary surgery. In the adjusted model, higher age was a significant risk factor for omitting radiotherapy, sentinel biopsy, and adjuvant endocrine treatment.

Conclusions

This study emphasizes the need for greater awareness on the part of general practitioners to facilitate early diagnosis of breast cancer in elderly women as well as the necessity for implementation of good practice guidelines for this growing segment of the Swiss population.

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List of approved research projects in 2011

Total funds allocated: CHF 1,034,400.–

Ess Silvia M. | KFS 02864-08-2011 | CHF 82,500.–
Krebsregister St. Gallen-Appenzell, St. Gallen
The burden of metastatic breast cancer in Eastern Switzerland: a population-based study

Kuehni Claudia E. | KFS 02783-02-2011 | CHF 270,000.–
Bereich Internationale Gesundheit und Umwelt, Institut für Sozial- und Präventivmedizin, Universität Bern, Bern
Late mortality, second primary cancers and cardiovascular late effects in childhood cancer survivors: Swiss participation in the EU FP7 project "PanCareSurFup"

Martin Brian | KFS 02820-08-2011 | CHF 48,000.–
Arbeitsbereich Bewegung und Gesundheit, Institut für Sozial- und Präventivmedizin, Universität Zürich
Impact of physical activity on cancer mortality in Switzerland: results of a 30-year follow-up

Meier Christoph R. | 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

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

Rosemann Thomas | KFS 02818-08-2011 | CHF 157,300.–
Institut für Hausarztmedizin, UniversitätsSpital Zürich, Zürich
minSKIN – Does a multifaceted intervention improve the competence in the diagnosis of skin cancer by general practitioners? A randomized controlled trial

Spörri-Fahrni Adrian | KFS 02763-02-2011 | CHF 261,500.–
Institut für Sozial- und Präventivmedizin, Universität Bern, Bern
Privacy Preserving Probabilistic Record Linkage (P^3RL) for cancer epidemiology research

Presentation of approved research projects in 2011

Ess Silvia M. | **The burden of metastatic breast cancer in Eastern Switzerland: a population-based study** (KFS 02864-08-2011)
Duration: 02.01.2012 – 01.07.2013

Despite advances in early diagnosis and treatments, metastatic breast cancer (MBC) continues to be the leading cause of cancer-related mortality and premature mortality of women in Eastern Switzerland. About 10% of newly diagnosed breast cancer patients present with Stage IV disease, and an unknown number of patients initially diagnosed with regional-stage disease will develop MBC. In fact, the majority of patients with MBC were initially diagnosed with locoregional breast cancer. The prevalence of MBC in Switzerland is unknown but considered to be high, as patients may live with the disease for many years.

MBC is a heterogeneous disease that has a variety of clinical scenarios, ranging from solitary metastatic lesions to diffuse and multiple organ involvement. Improvements in survival of patients with MBC described in the literature are probably related to the development and widespread utilization of modern systemic therapies and modern diagnostic tools allowing the detection of early metastatic disease, which may be more responsive to treatment than late, advanced metastatic disease. Moreover, the recognition of a subset of patients, e.g., those with limited MBC benefiting from more aggressive multidisciplinary therapeutic approaches, has led the European Society of Medical Oncology (ESMO) to recommend new studies in order to evaluate the crucial issue of follow-up and the value of "screening" for limited metastases in asymptomatic patients.

The aim of this study is to gain insight into the burden of both synchronous and metachronous metastatic breast cancer in Eastern Switzerland and factors that influence survival. This region of the country comprises areas with different degrees of urbanization and therefore with more or less easy access to specialized oncological care. The specific objectives are: (1) estimate incidence (number of new cases), prevalence (number of patients living with the disease), and survival of MBC patients in Eastern Switzerland, (2) study tumour and patient characteristics associated with MBC, (3) analyse time to metastases, patterns of metastases, and survival according to biological breast cancer subtypes, (4) describe treatments of patients diagnosed with MBC according to tumour subtypes, metastatic sites, and number, as well as patient characteristics (age, comorbidities, sociodemographic factors), and (5) investigate survival differences between patients diagnosed with *de novo* MBC compared with patients who have completed primary treatment, after adjusting for tumour subtypes, metastatic sites, and patient characteristics.

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Kuehni Claudia E. | **Late mortality, second primary cancers and cardiovascular late effects in childhood cancer survivors: Swiss participation in the EU FP7 project "PanCareSurFup"** (KFS 02783-02-2011)
Duration: 01.07.2011 – 01.07.2014

Thanks to improved treatments strategies, more than 80% of all children diagnosed with cancer can now be cured. However, intensive treatment with radiation therapy and chemotherapy has side effects, which can occur decades later. This includes other cancers, cardiac disease and an increased overall mortality. PanCareSurFup, an international study supported by the EU (FP-7) and the Cancer Research Switzerland foundation, investigates these problems.

In cohort studies conducted in several European countries, we are exploring the risk of these late effects and their causes. In case-control studies, we are assessing detailed treatment data, including doses and radiotherapy and chemotherapy. In interviews with patients we are assessing health relevant behaviours and environmental exposures.

Our results will help to improve treatment of current and future patients, with the goal to attain optimal cure rates with minimal late effects. In addition, the study will also help to plan screening for these late effects in former patients.

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Martin Brian | **Impact of physical activity on cancer mortality in Switzerland: results of a 30-year follow-up** (KFS 02820-08-2011)
Duration: 03.01.2012–02.01.2013

In Switzerland, each year around 35,000 individuals are diagnosed with cancer and 16,000 die. Physical activity has a wide range of positive health effects. For example, it is associated with a decreased cancer risk. For Switzerland, no estimates exist regarding the potential of physical activity for the prevention of cancer. The study aims to analyse the effects of physical activity on total and cancer mortality in almost 20,000 individuals over up to 30 years of follow-up. Physical activity data are available from two large cross-sectional studies. These have been linked with census and mortality data.

The study will provide evidence for the potential of physical activity promotion for cancer prevention at the population level. Further, it will create the basis for later cost estimates on the effects of inactivity related to cancer.

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Meier Christoph R. | **Use of metformin and the risk of colorectal, pancreatic, ovarian, and lung cancer** (KLS 02737-02-2011)
Duration: 01.07.2011–01.07.2012

In recent years, a mounting body of evidence suggested that use of metformin exerts protective effects against development of various malignant neoplasms. Only limited and/or conflicting data for pancreatic cancer and colorectal cancer is available and no observational evidence is available linking risk of lung or ovarian cancer to the use of metformin, despite encouraging results from basic science studies.

Using the well known General Practice Research Database (GPRD), we will conduct a series of case-control analyses to address the risk of pancreatic cancer, colorectal cancer, ovarian cancer, and lung cancer in relation to the use of metformin, other oral antidiabetic drugs, and insulin.

If we are able to demonstrate that use of metformin is indeed associated with a decreased risk of the malignancies investigated in this study, this drug may be used for chemoprevention in patients at high risk and/or further investigated as an adjuvant chemotherapeutic drug for treatment.

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Pestalozzi Bernhard | **End-of-life delivery of care patterns in cancer patients in Switzerland** (KLS 02738-02-2011)
Duration: 01.07.2011–01.01.2013

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 of all insured medical services provided to a patient, are well suited to examine treatment paths and patterns.

This study is a retrospective cohort study. First, with the help of the cancer registries Basel-Land/Basel-Stadt, Ticino, Valais, and Zurich, patients insured by the insurance company Helsana who died between 2006 and 2008 were identified as cancer patients. For these identified cancer patients, we are examining where, how, and how long they were treated during the last 1–6 months before death. The goal is to analyse whether cancer type, age, gender, or regional differences can be observed. In addition, this study will describe an "as-is" state, which can, after the introduction of the Diagnosis Related Groups (DRG) based system for hospital financing in Switzerland, serve as a reference for future comparison.

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Rosemann Thomas | **minSKIN – Does a multifaceted intervention improve the competence in the diagnosis of skin cancer by general practitioners? A randomized controlled trial** (KFS 02818-08-2011)
Duration: 01.04.2011–30.09.2012

In Switzerland the incidence of skin cancer is rising, and general practitioners (GPs) are often the first contact person for patients with suspicious skin lesions. In our study we are investigating whether a continuous education and training intervention improves GPs' competence in the diagnosis of skin cancer.

Seventy-eight GPs are randomly allocated to the education group or the control group (no education intervention). At the start, diagnostic competence in skin cancer is measured in both groups. General practitioners in the education group take part in continuous education and training on skin cancer for one year, provided by the study dermatologists. After one year, competence in skin cancer diagnosis is measured again in both groups to investigate if our education intervention improved the GPs' diagnostic competence.

Well-trained GPs have higher competence in assessing suspicious skin lesions and can refer patients rapidly to a dermatologist if necessary.

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140 Spörri-Fahrni Adrian | **Privacy preserving probabilistic record linkage (P^3RL) for cancer epidemiology research** (KFS 02763-02-2011)
Duration: 01.07.2011–01.07.2013

Record linkage is a potentially important source of valuable cancer epidemiological information, for example for shedding light on the effectiveness of screening methods or for evaluation of the long-term effects of cancer treatments. In the context of broadening concerns regarding confidentiality of patient medical data, record linkage methods have been expanded. Privacy preserving probabilistic record linkage (P^3RL) allows the linking of cancer-related data sources using important discriminating information such as patient name (encrypted) without a breach of confidentiality. This has the potential to transform cancer epidemiology research by making available anonymously vast amounts of cancer-related data that were not previously accessible.

The aims of this study are: (1) to examine the feasibility of P^3RL techniques (including data preprocessing, encrypting, and linkage), (2) to validate P^3RL comparing results to simulated and/or falsified original data, and (3) to obtain approval for the use of P^3RL from a Swiss federal authority.

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