

Cancer Research in Switzerland



A publication of Oncosuisse, Swiss Cancer League
and Foundation Cancer Research Switzerland on
their funded research projects
Edition 2006

Imprint

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Editorial

Since the first report on cancer research in Switzerland was published two years ago (*Krebsforschung in der Schweiz*, 2004), many steps forward have been achieved in the research and treatment of cancers. The partner organisations Oncosuisse, the Foundation Cancer Research Switzerland, and the Swiss Cancer League have not been idle. It is time, therefore, to report on the current state of cancer research in our country and to present the research projects that have been funded in recent years.

In the first part of this 2006 edition, specialists analyse the current situation in Switzerland. Playing an important role is *National Cancer Programme 2005–2010*, developed by Oncosuisse and published in early 2005 under mandate by the Federal Office of Public Health and the Conference of Cantonal Ministers of Public Health. What objectives were set out in the areas of prevention, early detection, treatment, quality assurance and epidemiology and cancer research? What has been achieved up to now? Also



Giorgio Nosedà



Thomas Cerny

discussed is the complex situation of patient-oriented research, which struggles with a whole string of financial, administrative, personnel and system-inherent problems. For this reason, it is of special concern to the partner organisations to increase support of epidemiological and patient-oriented research.

Part two of this report is devoted to research questions in basic research, clinical research, psychosocial research and epidemiology. The research projects that were funded from 2004 to 2006 are presented. A topic that stands out is “targeted therapies”. These therapies have changed the treatment of some types of cancer enormously in recent years and, at the same time, have raised a lot of questions. Research has to face up to these questions – also by means of new research projects.

All of this and further projects would not be possible, however, if the Foundation Cancer Research Switzerland (KFS) did not receive the generous support of countless donators. Every single franc donated contributes towards improving our knowledge of cancer and thus increases cancer patients’ chance of a cure or, at the least, alleviation of their suffering. To the donators we extend our sincere thanks for their support.

We would also like to thank the people that contributed to this second edition of “Cancer Research in Switzerland”, in particular the authors and the researchers.

Prof. Giorgio Nosedà
President
of Oncosuisse and
Foundation Cancer
Research Switzerland

Prof. Thomas Cerny
President
of Swiss Cancer
League

Research funding: Short-term for researchers, long-term benefit for patients

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In the past two years, the three partner organisations Oncosuisse, Foundation Cancer Research Switzerland and Swiss Cancer League contributed higher than ever support of cancer research in Switzerland: CHF 13.2 million in funding in 2004 and CHF 10.9 million in 2005. This large-scale commitment to cancer research is possible only thanks to the generosity of the charitable donors.

The core task of the three partner organisations Oncosuisse, Foundation Cancer Research Switzerland and Swiss Cancer League is to support industry-independent cancer research. Each of these organisations contributes to this joint goal in its own way, and the activities of all three organisations are coordinated.

- The *Foundation Cancer Research Switzerland* focuses its activities on procuring donations for the Oncosuisse research-funding programme.
- *Oncosuisse* has two main tasks: first, implementing the National Cancer Programme Switzerland, which was developed under a mandate by the Federal Office of Public Health and the Conference of Cantonal Ministers of Public Health and, second, providing research grants following the recommendations made by the Scientific Committee.
- The *Swiss Cancer League* supports cancer patients and their relatives, provides information, is active in cancer prevention, and funds cancer research. In addition to funding research projects, the Swiss Cancer League provides the Scientific Office. The Scientific Office handles the large part of the administrative tasks associated with research funding by all three partner organisations.

The research-funding policy of the partner organisations

All three organisations have made a commitment to donors to support the best research in international comparison. This requires an evaluation system that meets international standards. The important task of evaluating research proposals is the responsibility of the Scientific Committee (see p. 15). The Scientific Committee is supported operationally by the Scientific Office, which is responsible for organising the calls for research proposals and evaluation of the grant applications as well as for quality control of funded projects.

After the Scientific Committee has assessed the quality of submitted proposals, the boards of directors of Oncosuisse and the Swiss Cancer League make the grant decisions. Although the boards are free in their decision-making, they adhere to the rule that no research proposal will be selected for funding that has not been recommended by the Scientific Committee. Figure 1 shows the process of evaluation and approval for research proposals.

The funding policy of the boards of directors gives priority to patient-centred research. The purpose of this is, for one, to implement the National Cancer Programme, which stipulates a strengthening of public health research and clinical research. For another, this priority meets the needs of patients, who are dependent on the funding of industry-independent cancer research, so that diagnostic methods and therapeutic measures can be optimised and developed further. Support for treatment optimisation studies is therefore a main priority for the partner organisations.

Dr. rer. nat. Rolf Marti

Rolf Marti has headed the Scientific Office of the Swiss Cancer League since 2002 and is responsible for research funding. Marti is a member of the managing board of the Swiss Cancer League. One of the main focuses of his work is research policy.

Figure 1

How is a research proposal evaluated?

The research proposal is submitted to and recorded by the Scientific Office of the Swiss Cancer League.



The proposal is assigned to two members of the Scientific Committee (WiKo) who are experts in the special field (for example, psycho-oncology or basic research).



The two members of the Scientific Committee recommend external reviewers.



The external reviewers are asked to evaluate the proposal.



The external reviewers evaluate the proposal; four to six reviews are obtained for each proposal, with two of these reviews being prepared by members of the Scientific Committee.



The Scientific Office creates a file containing all of the reviews.



The Scientific Committee discusses the proposal at its biannual meeting.



After the Scientific Committee meeting, the proposals are ranked according to the Scientific Committee's recommendations.



The ranking list goes to the boards of Oncosuisse and the Swiss Cancer League. The boards decide what proposals will be awarded grants.



The applicant is informed of the decision; the reviews are made available to the applicant if desired.

So that priorities do not remain mere intentions, a quota was set for the allocation of funding: 60% is to go to patient-centred research. In addition, programmes were launched to support clinical research in international collaborations and to create incentives for knowledge transfer between different research areas and special fields (see the article by Thomas Cerny, p. 20, and the article on CCRP and ICP projects, p. 30).

What projects receive funding, and how much funding do they receive?

About 80% of the grant money goes to projects in independent project research; 15% of the funds go to research projects in the Collaborative Cancer Research Projects (CCRP) and International Clinical Cancer Research Group Projects (ICP) programmes, and 5% goes to scholarships and other projects. This allocation has remained constant in the past few years.

Altogether, funds for independent project research have increased by more than 40% (annual average 2001–2003: CHF 6.8 million; 2004–2005: CHF 9.6 million). For this reason, funding for projects in basic research has increased slightly, in spite of preferential support for patient-centred research projects, from CHF 4.4 million per year (2001–2003) to CHF 5.1 million (2004–2005). Nevertheless, a great many of the projects in basic research selected by the Scientific Committee for approval by the boards of directors could not be supported.

Owing to the new allocation quota adopted, the funds for patient-centred research have almost doubled, from CHF 2.4 million per year (2001–2003) to CHF 4.5 million per year (2004–2005). With very few exceptions, it was possible to fund all projects that the Scientific Committee judged worthy of support.

Research support through the cantonal cancer leagues

In 2005 the Swiss Cancer League conducted a survey on research funding by the cantonal cancer leagues. The aim of the survey was to obtain an overview of the research funds provided by the cantonal cancer leagues. The Swiss Cancer League also wanted to find out how the cantonal cancer leagues handle calls for proposals and evaluation of grant applications and according to what criteria they award grants.

In brief, the survey results show that the cantonal cancer leagues provided a total of CHF 4.13 million for research. Eighty-three per cent of the research funding was provided by the four biggest cantonal cancer leagues – Basel, Bern, Geneva, and Zurich, which each granted CHF 500,000 annually (Figure 2). Sixty-five per cent of the grant applicants received grants, and 42% of the amount of funding applied for was granted.

All of the cantonal cancer leagues provided the grants to institutions in their canton or region or to researchers that hail from their region. The different cantons have very different priorities for the allocation of research grants. Some cantons support young researchers, while others fund psychosocial research exclusively. Independent project research gets the lion's share, but provision of funds to the cancer registries is also subsumed under research support. While most of the cantonal cancer leagues do not seek closer cooperation with the Scientific Office of the Swiss Cancer League, they would like to see improvements in the mutual exchange of information.

Figure 2
Average annual spend of the cantonal cancer leagues on research (average of spend in 2003 and 2004)

Cantonal cancer league	Total spend (in CHF)
Thurgau	5,000
Zug	30,000
Aargau	63,250
Ticino	88,400
Neuchâtel	169,000
St. Gall-Appenzell	375,000
Bern	600,000
Basel	776,850
Geneva	792,750
Zurich	1,230,450

The survey also determined what cantons had received grants from the three partner organisations from 2000 to 2004. It is evident, although not surprising, that especially large grants went to cantons where cancer-specific research institutes are based – for example, the Swiss Institute for Experimental Cancer Research (ISREC) or the Swiss Institute for Applied Cancer Research (SIAC) (see Figure 3).

Figure 3

Distribution of cancer research funding to the cantons, 2002–2004

(Oncosuisse/Foundation Cancer Research Switzerland and Swiss Cancer League)

Canton		Number of projects	Spend in thousand CHF	Per cent of total spend	
AG	Cantonal hospitals, UAS, PSI	11	581	83	
	Scholarships and awards	2	118	17	
	Total	13	699	2	
BE	SIAK / IBCSG	16	2,001	32	
	University, Inselspital	31	3,795	61	
	Scholarships and awards	9	399	6	
	Total	56	6,195	13	
BL/BS	FMI	12	2,187	26	
	University	37	6,072	71	
	Scholarships and awards	3	268	3	
	Total	52	8,527	19	
GE	University	33	5,066	100	
	Total	33	5,066	11	
SG	Cantonal Hospital	4	342	93	
	University	1	5	1	
	Scholarships and awards	1	20	5	
	Total	6	367	1	
TI	Hospitals	14	2,505	80	
	IOSI / SENDO / IELSG	21	540	17	
	Scholarships and awards	3	100	3	
	Total	38	3,145	7	
VD	ISREC	31	6,331	48	
	University / CHUV	41	6,314	48	
	Scholarships and awards	7	560	4	
	Total	79	13,205	29	
VS	Screening programme	2	95	39	
	Scholarships and awards	1	150	61	
	Total	3	245	1	
ZH	ETH	12	2,901	34	
	University	29	5,359	62	
	Scholarships and awards	4	337	4	
	Total	45	8,597	19	
Total spend			46,046	100	

Abbreviations

AG UAS = University of Applied Sciences
PSI = Paul Scherrer Institute

BE SIAK = Swiss Institute for Applied Cancer Research
IBCSG = International Breast Cancer Study Group

BL/BS FMI = Friedrich Miescher Institute

TI IOSI = Oncology Institute of Southern Switzerland
SENDO = Southern European New Drug Organisation
IELSG = International Extranodal Lymphoma Study Group

VD ISREC = Swiss Institute for Experimental Cancer Research
CHUV = Centre Hospitalier Universitaire Vaudois

ZH ETH = Swiss Federal Institute of Technology Zurich

in thousand CHF 0 5,000 10,000 15,000

Foundation Cancer Research Switzerland (KFS) celebrated 15 years

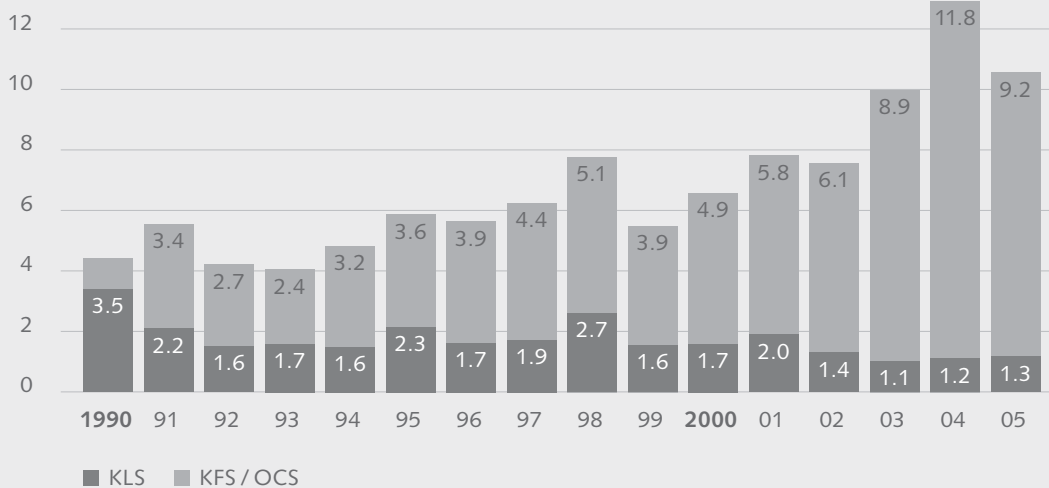
Cancer Research Switzerland (Krebsforschung Schweiz) was founded as an association in 1990. At that time, it had become apparent that a number of cancer research organisations were each planning their own charitable donation drives. The heads of the various organisations were in agreement that multiple individual drives were not the best way to raise funding for cancer research. For this reason, they founded Cancer Research Switzerland in order to present one joint front to potential charitable donors and thus acquire more funding for research support.

This goal was achieved and even exceeded in the past years. In 1995, Cancer Research Switzerland raised CHF 3.6 million, in 2000 CHF 4.9 million and in 2005 CHF 9.2 million for cancer research – a new record amount.

In 2000, Cancer Research Switzerland became a foundation. The foundation provides funding to Oncosuisse, which gives grants to researchers following the recommendations of the Swiss Cancer League Scientific Committee.

Direct cancer research spend by partner organisations, Swiss Cancer League (KLS) and the Foundation Cancer Research Switzerland/Oncosuisse KFS/OCS, on research projects (independent projects, research programmes and scholarships) since the founding of Cancer Research Switzerland in 1990

Spend (in million CHF)





Fall 1, 2006, 112 x 88 cm

Support of cancer research in Europe

How strongly does Switzerland support cancer research as compared to other countries? A survey conducted by the European Cancer Research Managers Forum (ECRM) investigated cancer research funding in the fiscal year 2002/2003 in 31 European countries (*ECRFS, European Cancer Research-Funding Survey*). The ECRM was particularly interested in comparing charitable and governmental cancer research funding. Since Switzerland was unfortunately not included in the survey, the Scientific Office of the Swiss Cancer League examined cancer research funding in Switzerland, in order to be able to draw a comparison with the European countries in the ECRFS survey (see Figure 4).

Figure 4
Ranked direct cancer research spend per capita in 2002–2003 (ECRFS survey), with Europe and USA for comparison

Rank	Spend per capita/EUR
1. United Kingdom	6.52
4. Germany	4.31
6. France	4.05
10. Finland	2.99
12. Italy	1.32
25. Austria	0.08
Average per capita spend, entire Europe	2.56
Switzerland	2.25
United States	17.63

Example: Per capita spend on cancer research in the United States is EUR 17.63.

In Switzerland, an annual total of EUR 2.25 per capita is invested in cancer research. This is slightly below the European average; in the statistics of the ECRFS, Switzerland would follow Finland, in 12th position. In total, the 31 European countries spend EUR 1.43 billion on cancer research every year. Charities account for just over 50% of this funding. This is also the case in Switzerland.

Research funding – the figures

In 2004 and 2005, the total spend on cancer research for the partner organisations was CHF 12.1 million annually (2004: CHF 13.2 million; 2005: CHF 10.9 million). Eighty per cent of funds went into independent project research. On average, 80 of 158 research proposals received funding each year, or 51%. In total, 25% of the funding applied for was granted (total applied for: CHF 48.2 million; granted: CHF 12.1 million). Oncosuisse and the Foundation Cancer Research Switzerland contributed 87% of the granted funding, and Swiss Cancer League contributed 13%.

Research funding: an overview

Number of grant applications submitted and amount applied for; number of the grants and amounts granted in 2004 and 2005 (all research areas)

	Independent project research	Scholarships	Research programmes (ICP / CCRP)	Other*	Total	
2004						
Number of grant applications	104	13	13	20	150	<p>82 4 11 3</p>
Number of grants	62	9	2	19	92	
Amount applied for (in thousand CHF)	26,606	962	20,501	509	48,578	
Amount granted (in thousand CHF)	10,809	541	1,500	393	13,243	
Proportion of total funds (in per cent)	82 %	4 %	11 %	3 %	100 %	
2005						
Number of grant applications	138	3	6	19	166	<p>78 3 15 3</p>
Number of grants	44	3	2	19	68	
Amount applied for (in thousand CHF)	36,437	410	10,648	443	47,938	
Amount granted (in thousand CHF)	8,472	377	1,687	376	10,912	
Proportion of total funds (in per cent)	78 %	3 %	15 %	3 %	100 %	
Average per year (2004 and 2005)						
Number of grant applications	121	8	9.5	19.5	158	<p>80 4 13 3</p>
Number of grants	53	6	2	19	80	
Amount applied for (in thousand CHF)	31,522	686	15,574	476	48,258	
Amount granted (in thousand CHF)	9,640	459	1,594	385	12,078	
Proportion of total funds (in per cent)	80 %	4 %	13 %	3 %	100 %	

■ Independent project research ■ Scholarships ■ Research programmes (ICP and CCRP) ■ Other

* Granted funding for scientific conferences, workshops, European organisations, research institutions in developing and threshold countries

Distribution of spend for independent research projects

The partner organisations contributed an average of CHF 9.64 million per year to independent project research (2004: CHF 10.8 million; 2005: CHF 8.5 million). Per year, an average of 53 out of 121 submitted proposals were funded, at a rate of 44%. In total, 31% of the funding applied for was granted (total applied for: CHF 31.5 million; granted: CHF 9.64 million).

Most of the demand for research funds came from biomedical research: 63% of research proposals for independent projects came from this sector. Only 26% of the funding applied for was granted (2004: 36%; 2005: 18%). In the area of clinical research, 44% of funds applied for were granted.

The low “success” rate for basic research projects does not mean that the research proposals submitted were of low quality. The reason rather is the quota rule, which is intentionally designed to strengthen funding for patient-centred research. Of a total of 81 projects in basic research that the Scientific Committee recommended for funding, 31 could not be funded. In patient-centred research, only 5 out of 61 projects recommended by the Scientific Committee did not receive funding.

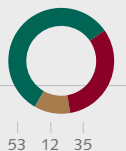
Distribution of spend for independent research projects

	2004	2005	Average per year
Biomedical research			
Number of proposals submitted	59	83	71
Total amount applied for (in thousand CHF)	16,968	22,715	19,842
in per cent	64%	62%	63%
Number of proposals granted	32	18	25
Total amount granted (in thousand CHF)	6,060	4,180	5,120
in per cent	56%	49%	53%

Clinical research			
Number of proposals submitted	31	34	33
Total amount applied for (in thousand CHF)	7,118	8,062	7,590
in per cent	27%	22%	24%
Number of proposals granted	21	18	20
Total amount granted (in thousand CHF)	3,379	3,371	3,375
in per cent	31%	40%	35%

Psychosocial research, epidemiology			
Number of proposals submitted	14	21	18
Total amount applied for (in thousand CHF)	2,520	5,660	4,090
in per cent	9%	16%	13%
Number of proposals granted	9	8	9
Total amount granted (in thousand CHF)	1,370	921	1,146
in per cent	13%	11%	12%

All projects			
Number of proposals submitted	104	138	121
Total amount applied for (in thousand CHF)	26,606	36,437	31,522
Number of proposals granted	62	44	53
Total amount granted (in thousand CHF)	10,809	8,472	9,641



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Criteria for good cancer research

The Scientific Committee of the Swiss Cancer League evaluates research proposals according to the following decisive criteria:

Significance Does the project contribute to improved understanding of causes, prevention or treatment of cancer?

Originality or socioeconomic relevance Is the research original (basic research) and/or up to date, and does it have socioeconomic significance (clinical or epidemiological research)?

Methodological approach Are the research strategies and methodologies chosen the most appropriate ones for realisation of the project?

Feasibility Is the project feasible in terms of the financial, staff-related and organisational situation?

Record of research achievement What tangible research contributions has the applicant (or group of applicants) made; what is the quality and significance of published work?



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The Scientific Committee

The Scientific Committee is responsible for evaluating the research proposals submitted to OncoSuisse and the Swiss Cancer League by researchers seeking grants for research projects. Evaluation follows strictly defined criteria. The central question is always whether and in what context a research project can advance our understanding of cancer causes, prevention or treatment.

The members of the Scientific Committee are respected scientists who are experts in the fields relevant to cancer research. By having all of the research fields represented in the one committee, rather than forming specialised subcommittees, we seek to promote attention to research trends in all areas. All members of the Scientific Committee have outstanding achievement records. They serve for three years and can be re-elected twice.

In addition to the Scientific Committee president, Professor Martin F. Fey (former president up to the end of 2005 was Professor Bernhard Hirt), representatives of the following research areas make up the Scientific Committee:

- Biomedical research (3 members)
- Patient-centred clinical cancer research (2)
- Laboratory-based clinical cancer research (2)
- Epidemiology/cancer prevention (2)
- Psychosocial and other cancer research (public health research) (2)
- Collaborative cancer research projects (2)

The Scientific Committee meets twice a year. At the meetings, applications for research grants that have already gone through a peer review process are discussed at length. The result of the discussions is a ranked list of the proposals that the Scientific Committee recommends to the board for granting approval. In most cases, the board follows the committee's recommendations; unfortunately, however, it is never possible to provide funding for all of the recommended research projects.

Members of the Scientific Committee 2004–2005

Prof. Dr. Dr. Thomas Abel
Department of Social and Preventive Medicine
(ISPM) University of Bern
Bern
since 2004

D^r Ellen Benhamou
Département de santé publique
Institut Gustave Roussy
Villejuif, France
since 2003

PD Dr. med. Stephan Bodis
Institute of Radiooncology
Cantonal Hospital of Aarau
Aarau
since 2000



President
of the Scientific Committee
Prof. Dr. med. Martin F. Fey

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Prof. Fred Th. Bosman
Institute of Pathology
Centre Hospitalier Universitaire Vaudois (CHUV)
Lausanne
1997–2006

Prof. Dr. Peter de Jonge
Dept. of Internal Medicine and Dept. of Psychiatry
University of Groningen
Groningen, Holland
since 2006

Dr. Maurizio D'Incalci
Department of Oncology
Mario Negri Institute for Pharmacological Research
Milan, Italy
since 2002

Prof. Dr. med. Martin F. Fey
Institute of Medical Oncology
University Hospital Bern (Inselspital)
Bern
President of the Scientific Committee since 2006

Dr. med. Silvia Franceschi
Infections and Cancer Epidemiology Group
International Agency for Research on Cancer (IARC)
Lyon, France
1997–2005

Prof. Dr. med. Marcus Groettrup
Division of Immunology, Department of Biology
University of Konstanz
Konstanz, Germany
2000–2005

Dr. Brian A. Hemmings
Friedrich Miescher Institute (FMI)
Basel
since 2003

Prof. Dr. phil. Bernhard Hirt
Virologist, Professor Emeritus
Lausanne
President of the Scientific Committee 2002–2005

Prof. Dr. med. Alexander Kiss
Division of Psychosomatic Medicine
Department of Internal Medicine
Kantonsspital Basel
Basel
1997–2006

Prof. Dr. med. Serge Leyvraz
Fondation du Centre Pluridisciplinaire d'Oncologie,
Centre Hospitalier Universitaire Vaudois (CHUV)
Lausanne
1996–2004

Prof. Dr. Joachim Lingner
Swiss Institute for Experimental Cancer Research
(ISREC)
Epalinges
since 2003

Prof. Dr. med. Holger Moch
Institute of Surgical Pathology
University Hospital Zurich
Zurich
since 2006

Prof. Dr. med. Felix Niggli
Pediatric Hematology/Oncology
University Children's Hospital Zurich
Zurich
since 2002

PD Dr. med. Cristiana Sessa
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Bellinzona
since 2000

PD Dr. George Thomas
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Basel
2001–2004

Dr. phil. Peter Wellauer
Swiss Institute for Experimental Cancer Research
(ISREC)
Epalinges
1998–2004

“Funds are limited and should go to the best”

Interview: Rolf Marti, head of the Scientific Office, Swiss Cancer League, and Brigitte Walser, editor, Swiss Cancer League

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At the beginning of 2006, Professor Bernhard Hirt handed over his post as president of the Scientific Committee to Bern-based oncologist Professor Martin F. Fey. Hirt and Fey met with us for the following conversation.

Professor Hirt, as president of the Scientific Committee you were in a position to decide what type of cancer research would be carried out.

Bernhard Hirt That is not correct. It is the board and not the Scientific Committee that makes the decisions on what type of research will be funded. The committee's task is to assure the quality of the research. However, the two groups are in communication with each other, of course. The funds are limited, and they should go to the best. This is not an easy task.

What constitutes good cancer research, Professor Fey?

Martin F. Fey Research that advances understanding, starting from the problem of cancer biology on up to the patient with cancer. It is not only projects that aim to develop a new treatment or drug in two years' time that deserve support. What is needed is a good mix of basic research, laboratory-based research, applied research and clinical and psychosocial research, but epidemiology and prevention are also important.

Isn't clinical research always going short of funding?

Martin F. Fey Clinical research cannot be said to be generally underfunded or not active enough. The situation is, rather, that certain, often very expensive, studies are difficult to finance. Clinical research is not infrequently funded by industry, and the industry, of course, dictates the research topics. There are research projects that are of no interest to the indus-

try and therefore receive no industry support. But it is precisely these projects that sometimes examine important research questions. It is our task to support them.

Bernhard Hirt For the Swiss Cancer League, it is not true that clinical research receives too little funding. For the Swiss National Science Foundation, it is. The Swiss National Science Foundation (SNSF) is the largest funder of basic research. This is not a reproach – after all, I was in basic research myself. But it points out that the Swiss Cancer League has a special task. The SNSF does not have a mandate to conduct clinical research, whereas the Swiss Cancer League and Oncosuisse do. And both fulfil this task. The problem in the past few years was that the research proposals submitted were not of high enough quality. But the explanation for this is easy: it is mainly young researchers in basic research that receive funding.

Would you also give support to research projects in complementary and alternative medicine?

Martin F. Fey If the research design is scientific and evidence based, then yes, certainly. But this is not often the case. Two worlds collide here, and in some ways they can never meet. For if to us – with our knowledge and background – the methods chosen seem completely muddled, and the other side does not accept our methods, then the situation becomes difficult.

Bernhard Hirt Science is dependent on measurable outcomes. Even quality of life can be measured, I am sure, and I am also in favour of doing so. But if you posit a medication without knowing what it contains or what dosage should be given, then you cannot simply plan a clinical study on it.



New president:

Martin F. Fey

Professor Martin F. Fey grew up in Bern and completed a doctorate at the Faculty of Medicine at the University of Bern. Since 1993 Fey has been the director and head of the department of medical

oncology at the Inselspital (University Hospital Bern) and since 2001 co-director of the department for clinical research of the Faculty of Medicine at the University of Bern. To date, he has more than 160 publications to his name. In 1993 Fey received the Robert Wenner Award of the Swiss Cancer League. From 1994 to 2002 he was a member of the Scientific Committee. Fey lives in Zollikofen and is married and has two children.



Departing president:

Bernhard Hirt

In a farewell to Professor Bernhard Hirt, the president of the Swiss Cancer League, Professor Thomas Cerny, wrote:

"At our latest meeting on 7 November 2005 we said goodbye to Emeritus

Professor Bernhard Hirt, president of the Scientific Committee. Professor Hirt was a member of the board of the Swiss Cancer League and his departure leaves a big gap. His knowledge and management style contributed to the excellent reputation of the Scientific Committee. He was able to bring on board the best experts internationally. On the board, Professor Hirt was modest but determined and persuasive; he not only spoke for research topics but put forward very patient-oriented and far-sighted argumentation. His humour and on-target punchlines will be sadly missed, because using those he knew how to defuse overheated debate and prevent conflicts from arising altogether."

You are both very critical ...

Bernhard Hirt Not at all. We cannot ignore patients' desire for alternative methods. I know doctors that use a rigorously scientific approach in their own work but consult an alternative practitioner when they themselves fall ill. That's human nature. But it has nothing to do with science.

The Scientific Committee evaluates research proposals according to strict scientific criteria. Do potentially groundbreaking or original ideas even have a chance, with such strict controls?

Martin F. Fey I have to start by saying that absolutely groundbreaking ideas are not all that common. There are some, and there are certainly also some researchers with groundbreaking ideas that remained unrecognised for years or even decades. But we cannot fund all proposals just to ensure that the one really brilliant idea is not excluded. Even flashes of genius have an underlying solid basis, and if this is apparent, then we support also unusual approaches.

Bernhard Hirt There is a great danger that genuinely original ideas will not be recognised. Breakthroughs cannot be predicted, after all. But as Martin Fey says, a groundbreaking idea is rare. In evaluating grant applications, we also pay attention to the researcher's scientific career. If that sounds promising, then we will also recommend approval of an original proposal.

Martin F. Fey Another very important criterion is whether a research project is at all feasible. No matter how ingenious an idea is, it is pointless if it cannot be implemented.



Berg 5, 2003, 130 x 190 cm

Professor Fey, you head a department at the Inselspital (the University Hospital in Bern), you conduct research, and you are active in several organisations. How do you reconcile all of these activities?

Martin F. Fey I have absolutely no idea (laughs). No, you have to be organised. And I give careful consideration to what I want to participate in and what not. Moreover, our hospital has several highly experienced senior doctors that take on many tasks under their own responsibility.

Bernhard Hirt Looking back, I would say that the workload was very often at the upper limit of what was possible. On the other hand, while collaborating in a Scientific Committee means investing a great deal, you also profit from it, and that in turn helps you in other activities.

Martin F. Fey Exactly. You could call collaborating in a scientific committee a form of legitimate and legal industrial espionage. But of course one should not abuse this privilege, and we don't. But participation allows you to build up a network of knowledge and contacts.

What aims have you set for the committee, Professor Fey?

Martin F. Fey I want to maintain the quality and the objectivity that Professor Hirt mentioned. Money is tight, and it should be spent only on something that is worthwhile.

Supporting patient-centred research

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In addition to providing broad research funding as up to now, the Swiss Cancer League (KLS) and its partner organisations aim to provide strong support specifically to research projects that focus on cancer prevention or the immediate needs of patients. With this, the KLS not only upholds a tradition that has existed since the organisation was founded but also accords with the wish of many charitable donors. To this purpose the KLS has taken a number of measures to strengthen its support of patient-centred research. We are now seeing the first results of these measures.

The KLS works towards a world in which

- fewer people develop cancer
- fewer people suffer and die from the consequences of cancer
- more people are cured of cancer
- patients and their relatives receive support and help during all phases of the disease and the dying process

All of the activities of the KLS focus on people, especially cancer patients and their relatives. We apply our maximum of “putting people first” also to the research projects that receive support from the KLS. For this reason, the KLS board decided in 2004 to give funding priority to patient-centred research.

Measures to support patient-centred research

Patient-centred means that the needs of patients have top priority and that the results of research projects have direct benefits for prevention, diagnosis or treatment of cancer (applied research). Patient-centred research combines research projects from all areas of clinical research, nursing and care research, epidemiology, psychosocial research, prevention and public health. Patient-centred research is essentially complemented by basic research, which studies the biological and molecular basis of the genesis of cancer.

To support patient-centred research, the KLS has instituted two measures:

New 60% quota 60% of all research funds are to be spent specifically for patient-centred research that is conducted without industry sponsoring (independent research), with 40% going to clinical research and 20% to nursing and care-giving research, epidemiology, prevention, public health and psychosocial research. 40% of the research funds are earmarked for basic research. Formerly, the percentages were the opposite: about 60% of the funds went to basic research and only 40% to patient-centred research.

Streamlined application process The grant application procedure for researchers planning a patient-centred research project has been simplified. Instead of submitting a comprehensive, detailed research proposal, researchers submit a brief description of the research project (letter of intent), which is then evaluated by experts on the Scientific Committee. If

the experts assess the project as potentially worthy of funding, the researchers are invited to submit a full proposal. This two-step process saves researchers from having to spend time and effort on grant applications that in the final evaluation have no chance of being approved. If a grant applicant is invited based on the letter of intent to submit a full proposal but is not successful, the Swiss Cancer League will contribute to the expenses for the elaboration of the full proposal (Table 1).

Additionally, Oncosuisse has developed two special programmes that benefit patient-centred research directly. Collaborative Cancer Research Projects (CCRP) support direct collaboration between basic and clinical researchers with the goal to make new findings from the laboratories immediately and directly available to clinicians in bedside patient care.

The International Clinical Collaborative Projects (ICP) support already existing, successful, international research collaborations.

Initial successes

The measures to support patient-centred research have already shown initial positive results. In 2001, 2002 and 2003, Oncosuisse and the Swiss Cancer League directly funded independent research projects with a total spend of CHF 20 million, with 65% going to basic research, 25% to clinical research, and 10% to epidemiology and psychosocial research. In 2004 and 2005, research projects were granted CHF 19 million, with 53% going to basic research but a respectable 35% to clinical research and 12% to epidemiology and psychosocial research (see Table 2).

The goal to invest 40% of funding in clinical research and 20% in epidemiology and psychosocial research has not yet been fully achieved. One reason is that in these areas currently, too few grant applications

are submitted that meet the high quality standards. In future, the partner organisations want to attempt targeted outreach to researchers conducting patient-centred research, inviting them to submit grant applications or letters of intent. Information on funding opportunities offered by the Swiss Cancer League is therefore being provided on the websites and in the publications of relevant institutions and organisations.

The research projects in the area of patient-centred research that receive grants are very diverse. The following are examples of research questions that are being examined in the research projects:

Clinical research

- How does hepatocellular carcinoma develop as a result of hepatitis C virus infection?
- What are the side effects of proton radiation therapy in children, and how does it affect the children's quality of life in the long term?
- What is the influence of preventive and therapeutic measures in prostate cancer on prostate-specific antigen (PSA) levels and the survival of the tumour cells?
- Are there factors that predict the development of a Kaposi's sarcoma that develops in HIV-positive patients taking antiretroviral drugs?
- What tissue changes occur in cases of primary mediastinal B-cell lymphoma, and what are the effects of standard therapy?

Table 1
Letters of intent submitted (number of and requested amount) and approved for grants

<i>(Amount in thousand CHF)</i>	April 2004		Oct. 2004		April 2005		Oct. 2005	
	Number	Amount	Number	Amount	Number	Amount	Number	Amount
Letters of intent submitted	3	314	5	1,255	17	3,283	16	2,870
Invited to submit full proposal	3		3		9		7	
Full proposal submitted	3	406	1	334	9	1,834	6	1,809
Full proposal approved for grant	3		1		5		3	
Amount granted		307		266		917		605

Psychosocial research

- What are the effects and benefits of psychotherapy (individual or group psychotherapy) for cancer patients who are experiencing psychological stress?
- Yes or no to stem cell transplantation – what aspects have to be taken into consideration regarding additional therapies?
- What is the quality of life of children who develop cancer as infants or toddlers?
- Palliative treatment of cancer patients: what is the status quo in Switzerland, and how can the situation be improved?
- How can the advantages and disadvantages of standard therapies and treatments in the context of scientific studies be better communicated to patients?

Epidemiology and prevention

- Are the incidence and survival chances of children with leukaemias or lymphomas associated with socioeconomic status?
- What are the roles of diet, alcohol consumption or genetic factors in the development of various cancers?
- How do familial, genetic factors influence the breast cancer risk of women in the Canton of Geneva?

Why should patient-centred research receive particular support?

The Swiss Cancer League and Oncosuisse receive considerably more grant applications from researchers in basic research than from researchers that conduct patient-centred research. There are several reasons for this. Clinical research projects are often complex and as a rule planned over several years, and they are therefore very expensive. Without substantial grant monies, it is almost impossible to finance clinical projects.



Gletscher 3, 2005, 144 x 108 cm

A further obstacle for research projects is the enormous administrative and formal effort that these projects require today. Each project has to be assessed by at least one ethics committee, and extremely high safety standards have to be adhered to. The rigid regulation of liability for study participants can hinder a project massively or lead to failure already in the planning stages. In the past few years, pharmaceutical industry-independent clinical research has almost come to a complete halt – which is an irresponsible loss of quality for clinical medicine altogether. We are therefore fighting red tape, unrealistic safety concerns and the overwhelming tendency on the part of diverse agencies and bodies to patronise patients.

Clinical research is conducted mostly by physicians that also work in hospitals treating patients and training other doctors. The double burden of practising medicine and conducting research is so great that many physicians do not even consider engaging in research activities or do so only when there is a hope for support. Additionally, career prospects are clearly worse for practising physician researchers than for physicians that work exclusively in research. Under these circumstances, it is often hardly possible or reasonable to develop, conduct and evaluate a clinical research project.

Table 2
Distribution of grants for independent research projects, by research area and year

	2001	2002	2003	2004	2005	First half of 2006
Basic research						
Total in million CHF	4.31	4.02	4.75	6.0	4.18	3.84
In per cent	58 %	70 %	65 %	56 %	49 %	50 %
Clinical research						
Total in million CHF	2.0	1.0	2.19	3.31	3.36	2.37
In per cent	27 %	18 %	30 %	31 %	40 %	31 %
Psychosocial research/epidemiology						
Total in million CHF	1.12	0.67	0.36	1.37	0.92	1.48
In per cent	15 %	12 %	5 %	13 %	11 %	19 %
All projects						
Total in million CHF	7.43	5.7	7.3	10.7	8.5	7.7
In per cent	100 %	100 %	100 %	100 %	100 %	100 %

A further reason for the shadowy existence of independent clinical research is the fact that disciplines like nursing and care-giving research or psychosocial research have long been regarded as “soft” research areas that tended to be sniggered at until just a few years ago. They are still hardly represented at Switzerland’s universities, there is no community of researchers in these areas, and published results do not find sufficient recognition by other researchers or are even ignored altogether.

However, clinical and patient-centred research makes an important contribution towards maintaining and improving quality in modern medicine. Clinical research, for example, examines whether standard therapies fulfil efficacy and safety criteria or whether new therapies are expedient and cost effective. While clinical research projects such as these are rarely innovative or original, they are of essential importance for providing optimal patient care.

More than research funding

In addition to supporting research directly, through sharing the cost of selected research projects, the Swiss Cancer League takes a stand for patient-centred research also in health policy. In the summer of 2006, the KLS issued position statements relating to the revision of the Federal Law on Patents for Inventions and the planned Law on Research in Human Subjects. In both statements, the KLS has emphasised that independent, industry-independent research in Switzerland should not be hindered. At the same time, the dignity and personality of study participants must be protected. Research with human subjects or human tissues can yield ethically acceptable results only if it is also being done in the interest of the people involved.



Prof. Dr. med. Thomas Cerny

Thomas Cerny is Head of Oncology/Haematology at the Cantonal Hospital of St. Gall and Professor of Medical Oncology at the University of Bern. In addition to serving as president of the Swiss Cancer League, Cerny is the Swiss editor of

the European journal *Oncology*. Cerny has published many professional articles, heads up national and international research projects and is a member of national and international professional associations that are active in the development of new drugs for cancer treatment and prevention.

National Cancer Programme Switzerland 2005–2010:

The state of affairs

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The Federal Office of Public Health (FOPH) and the Conference of Cantonal Ministers of Public Health (GDK) mandated OncoSuisse to develop a national cancer programme. OncoSuisse presented *National Cancer Programme Switzerland 2005–2010* to the authorities and to the wider public at the beginning of 2005. The programme met with a positive response by the authorities, who then charged OncoSuisse with proposing a short priority list for further action. The reason for this may have been the political necessity to keep things simple, because it is easier to plead a case politically using individual catchwords and issues than it is on the basis of long lists. OncoSuisse delivered the priority list in October 2005, and it was accepted by the political platform *Dialog Nationale Gesundheitspolitik* (National Health Policy Dialogue)¹ as a possible framework for action. The priorities defined for each of the subareas met with broad approval, and they form the basis for further implementation. It is high time, then, to ask what has happened since.

The FOPH is currently drawing up an overview of the activities of the FOPH and the federal government in the area of cancer that makes it possible to describe the situation in context. The overview reveals an impressive list of activities across the entire Federal Administration. The FOPH wants to extend the overview to include possible contributions that the FOPH can make towards implementing the National Cancer Programme Switzerland. This intention alone marks the new ranking of the fight against cancer on the government agenda. But to even the general reader, it is apparent that what is largely lacking is coordination.

Prevention

From an overarching strategic perspective, the FOPH is drawing up recommendations for a national prevention policy (*Neuregelung Prävention und Gesundheitsförderung*, PGF2010)², which – if approved by the Federal Council – could lead to a national law on prevention and health promotion. This would provide a legal basis for a health policy where health promotion and prevention are of equal importance to treatment. At the level of practical content, the prevention concept developed by the Swiss Cancer League (KLS) has been mentioned as a possible useful basis, but up to now it has not been integrated in the work at the federal level. Consequently, the federal government's priority remains the development and implementation of a national tobacco strategy with the primary aim to protect non-smokers. The federal government supports the cantons in this area, without issuing directives. It is hoped that multiple and heterogeneous decisions on the part of the cantons will at last make a federal solution necessary and politically acceptable. The non-governmental organisations and particularly the cantonal cancer leagues are not included in this scenario, but they are obviously facing a huge task.

Prof. Dr. med. Reto Obrist

Reto Obrist is director of OncoSuisse (part-time) and was responsible for drawing up “National Cancer Programme Switzerland 2005–2010”. Obrist is FMH specialist (Swiss Medical Association) in internal medicine and oncology-haematology and heads the Department of Oncology of the Canton of Valais.



Gletscher 2, 2005, 144 x 108 cm

Early detection

The situation regarding early detection is considerably less visionary. Several applications have been submitted to the *Eidgenössische Leistungskommission* (ELK) in favour of mammography, colorectal and cervical screening, vaccination against human papillomavirus (HPV), and genetic testing (on behalf of the Federal Department of Home Affairs, the ELK decides which medical services and medical drugs are to be reimbursed by health insurance companies or included on the list of “standard” services). While the FOPH processes the applications administratively, there is no policy on them, nor are there any strivings to form a policy. The early detection policy for cancer, which was set out by a broad-based working group, is being acknowledged but not pursued any further. This is in contrast to the Conference of Cantonal Ministers of Public Health, which is mostly in favour of the development of health technology assessment. Those cantons that have introduced

mammography screening are convinced by the evidence base for instituting breast cancer screening programmes and are hoping to convince other cantons to follow suit. In German-speaking Switzerland, the first cantons (St. Gall, Aargau) are on their way to having their own early-detection programmes; the work of the cantonal cancer leagues has been effective here. And evaluation results on the programmes in French-speaking Switzerland will be available soon, which will allow decision-making on the basis of Swiss data. Next year the ELK will have to once again evaluate whether health insurance companies should reimburse the cost of mammographies. Cantons that have not instituted early-detection programmes and the FOPH are keeping out of this discussion, even though it would be imperative for them to participate. Overall, however, the tone of the discussion has become more objective and the argumentation more balanced.

What stands out in the current situation is the lack of conceptual or operational leadership at the federal level. In the face of the cost relevance of the multiple early-detection measures (also outside the area of cancer), one can justifiably ask just who, then, is taking responsibility. The development of clear early-detection guidelines and procedures is desirable, so that recommendations can be made or decisions taken on the basis of accepted evaluations and insights. The early-detection commission, with commission members Oncosuisse and national partners, could serve as a medium here. The existing vacuum absolutely demands activity in this area.

Clinical quality assurance

Quality assurance of treatment and care of cancer patients is handed off to the cantons, even though there is a legal basis for national quality assurance programmes (Article 58 of the Federal Law on Sickness Insurance, KVG). Still, as a minimal activity and under parliamentary pressure (Motion SGK-N 04.3624 “Quality assurance and patient safety in the health care system”), proposals are worked out for the development of outcome indicators and procedures in interventional cancer therapy for which minimum number of incidences of treatment required for quality assurance could be instituted. As it has long been known that there is a relationship between quality and volume, this could, at last, result in enforceable changes in clinical practice. These steps accord with suggestions in the National Cancer Programme and certainly go in the right direction. They are also supported by many of the cantons.

Unfortunately, little is taking place in palliative medicine, in psychosocial support or on the issue of cancer survivors, a topic that will gain in importance and for this reason has been on the agenda elsewhere for a long time. For the activities of NGOs this opens up another wide field that requires urgent attention.

Cancer epidemiology

The cancer registries are undoubtedly a national task, but the data collection is largely financed by the cantons. The federal government is interested in national evaluation of these data (*fonction centrale* of the cancer registries) and is willing to finance this. For the next budget period, this is planned via research funding from the FOPH. While this does not secure the funding of the cantonal registries, it is hoped that this clear signal from the federal government will prompt the cantons to continue this – very heterogeneous – funding and perhaps even make it more homogeneous. The Conference of Cantonal Ministers of Public Health has issued a similar request to the cantons. In parallel, Oncosuisse and the Association of Swiss Cancer Registries are trying to drive forward the creation of a National Institute for Cancer Epidemiology and Registration (NICER). The aim is to establish a national institution that takes over the tasks of the “central function” and a networking function for all of the registries. Cross-connections with the Swiss School of Public Health and other institutions are currently being considered, but it is too early for concrete steps to be taken.

Research

In the National Cancer Programme, research was given a relatively minor priority (because of the mandate to develop a programme with a public health orientation). Nevertheless, there are currently some very important issues in the area of research. Key words here are the pending law dealing with biomedical research in human subjects, human tissue, and cells (*Humanforschungsgesetz*, HFG [Law on Human Research]) due to be passed in 2007; insurance protection for participants in clinical research (SAMW [Swiss Academy of Medical Sciences], industry); Biobank Suisse, which originated as an Oncosuisse project and is now a foundation in its own right; the forthcoming restructuring of clinical research funding from the State Secretariat for

Education and Research (SER) to the Swiss National Science Foundation (SNSF), with possible far-reaching consequences for some Oncosuisse members – namely, for the Swiss Institute for Applied Cancer Research (*Schweizerisches Institut für Angewandte Krebsforschung*, SIAK) and the Swiss Working Group for Clinical Cancer Research (*Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung*, SAKK); and, last but not least, the traditional heavy priority placed on funding research by Oncosuisse.

There is a new topic emerging that will have to be addressed in the next few years: the imbalance between industry-funded, publicly funded and third-party-funded clinical research. As a consequence of this imbalance, essential questions for society and the health care system are not being raised and therefore cannot be answered. In addition to aspects of drug therapy that are not commercially interesting (keyword therapy optimisation), the issues have to do with the situation of the health care system (health services research) and with quality in medicine. Here the grim battle concerning the allocation of scarce federal resources through the Swiss National Science Foundation plays a central role. The fact that funding has been allocated by far predominantly – with increasing demand – to basic science (the natural science foundation subjects) only exacerbates the problem. While it remains to be seen how this course could be corrected, from a higher-level perspective the necessity for a course correction seems clear.

Precisely because there is no coordination at the national level by a single body either within or outside the federal authorities and the Conference of Cantonal Ministers of Public Health for implementation of the National Cancer Programme, the overview prepared by the FOPH mentioned above is an important first step and a basis for further coordination at the federal level. After all, the plan foresees annual meetings on cancer activities in future, with the participation of all of the federal authorities involved. This means that the scourge of cancer is being tackled at the federal political and administrative level. This new priority ranking of the fight against cancer at the federal level has another side to it, however: the federal government is initially engaging in exploratory navel-gazing; joint aims or approaches together with the NGOs are currently not under discussion. But also for the NGOs there is still a lot to do. Oncosuisse and the Swiss Cancer League will analyse the obvious gaps and adjust future activity planning accordingly.



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- 1 «Nationale Gesundheitspolitik Schweiz»: The cantons (Conference of Cantonal Ministers of Public Health) and the Swiss government (Federal Department of Home Affairs) have met three times per year since 2004 to discuss health policy issues for which they carry joint responsibility. To this purpose, they each set up a managing committee and an office. For details (in German or French), see: www.bag.admin.ch/themen/gesundheitspolitik
- 2 For a factsheet on the FOPH project on a national law on prevention and health promotion, see: www.bag.admin.ch/themen/gesundheitspolitik

Greater collaboration in research

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With its two funding programmes, Collaborative Cancer Research Projects (CCRP) and International Clinical Cancer Research Groups (ICP), Oncosuisse supports research collaboration transcending the boundaries of disciplines, institutes and countries.

Collaborative Cancer Research Projects (CCRP)

Cancer research is often so complex that collaboration between different scientific areas and disciplines and institutions is expedient or necessary, even. Oncosuisse decided a few years ago to give targeted support to research collaboration in the form of CCRP (collaborative projects). In collaborative projects, valuable synergy develops between the various scientific disciplines and investigators with very different expertise. This synergy often accelerates knowledge transfer and also the conducting of the projects.

The CCRP idea stems from other countries in Europe and from the United States. There, for some time now, comprehensive research projects with a project duration of five or more years have been supported. In Switzerland traditionally – and including Oncosuisse and the Swiss Cancer League – funding is mostly given to projects that have a clearly formulated goal and a duration of maximum three years.

In the framework of a collaborative project, it is possible to subdivide a complex main project, which does not have to be written up to the very last detail, into numerous subprojects that are conducted at different institutions. This means that a large number of researchers can work towards one large goal, mutually exchange ideas and research results, and thus generate increased insights. Since launching the CCRP, Oncosuisse has provided a total of CHF 4.1 million in funding for four collaborative projects (2004 to mid-2006).

International Clinical Cancer Research Groups (ICP)

In the context of the ICP, Oncosuisse supports clinical cancer research specifically. This is urgently needed, because clinical research in Switzerland is faced with many obstacles. Clinical researchers in other countries can work with much larger case numbers, and in most countries the health systems are more centralised than in Switzerland. Both of these factors allow researchers to conduct studies more rapidly than would be possible in Switzerland.

Clinical research is a complicated undertaking that often can not really be funded on a project basis. The ICP programme is designed to help remedy this situation. The grants are earmarked for groups of clinical researchers that are international in make-up but have their coordinating centre or project management in Switzerland. Two examples of international research groups are the IBCSG (International Breast Cancer Study Group), which for over 20 years has been the world leader in the area of adjuvant postoperative therapies, and the IELSG (International Extranodal Lymphoma Study Group), founded eight years ago and based in Bellinzona, which comprises 35 institutions on three continents. The purpose of the ICP is to encourage Swiss oncologists to take leading roles in international projects.

An International Clinical Cancer Research Group receives annual funding of maximum CHF 125,000, or a total of CHF 500,000 over four years. There is interest in the ICP; the necessity is not disputed. Since initiating the ICP in 2003, Oncosuisse has supported six international projects with a total of CHF 2.8 million (2003 to mid-2006).

Ongoing projects of the Collaborative Cancer Research Projects (CCRP) and the International Clinical Cancer Research Groups (ICP)

CCRP

Primary central nervous system lymphoma: from an improved knowledge of its peculiar molecular and biologic feature towards the optimization of treatment (CCRP 01443-12-2003)

Dr. Francesco Bertoni

Laboratoire d'oncologie expérimentale

Istituto Oncologico della Svizzera Italiana (IOSI)

via Vela 6

CH-6500 Bellinzona

Duration: 1.8.2004 – 1.8.2006

CHF 450,000.–

In collaboration with:

- Prof. Adriano Aguzzi, Universitätsspital Zürich, Department Pathology, Zurich
- Prof. Emanuele Zucca, Istituto Oncologico della Svizzera Italiana (IOSI), Ospedale San Giovanni, Bellinzona
- Dr. Mariagrazia Ugucconi, Institute for Research in Biomedicine (IRB), Bellinzona
- Dr. Frank L. Heppner, Institute of Neuropathology (NPZ), Zurich
- Dr. Maurilio Ponzoni, Department of Pathology, Ospedale San Raffaele (HSR), Milano, Italy
- Dr. Andreas J. Ferreri, Department of Radio-Chemotherapy, Ospedale San Raffaele (HSR), Milano, Italy
- Dr. Marco Zaffalon, Istituto Dalle Molle di Studi sull'Intelligenza Artificiale (IDSIA), Manno, Switzerland
- Dr. Silvio Bicciato, Dip. Processi Chimici dell'Ingegneria, Università di Padova (UPD), Padova, Italy
- Dr. Luca Mazzucchelli, Istituto Cantonale di Patologia (ICPL), Locarno

The role of Wnt signalling in breast cancer

(CCRP 01445-12-2003)

Dr. Cathrin Brisken

Swiss Institute for

Experimental Cancer Research

ISREC

Chemin des Boveresses 155

CH-1066 Epalinges

Duration: 1.7.2004 – 1.7.2007

CHF 1,050,000.–

In collaboration with:

- Prof. Nancy Hynes, Friedrich Miescher Institute for Biomedical Research, Basel
- Dr. Maryse Fiche, Institut Universitaire de Pathologie, CHUV, Lausanne

Development of molecular strategies for therapeutic interference with glioblastomas

(CCRP 01613-12-2004)

Prof. Adrian Merlo

Neurochirurgische Klinik

Universitätsspital

Spitalstrasse 21

CH-4031 Basel

Duration: 1.1.2006 – 1.1.2009

CHF 1,276,200.–

In collaboration with:

- Dr. Brian Hemmings, Friedrich Miescher Institute for Biomedical Research, Basel
- Prof. Bernhard Bettler, Institute of Physiology, Pharmazentrum, University of Basel, Basel

ICP

Risk of cancer in persons infected with HIV

(ICP 01355-03-2003)

Dr. Silvia Franceschi

International Agency for Research on Cancer

120 Cours Albert Thomas

F-69008 Lyon, France

Duration: 1.1.2004 – 1.1.2008

CHF 500,000.–

In collaboration with:

- PD Dr. Christine Bouchardy, Registre genevois des tumeurs, Genève
- Prof. Fabio Levi, Registre vaudois des tumeurs, Institut universitaire de médecine sociale et préventive/CHUV, Lausanne
- Dr. Martin Rickenbach, Swiss HIV Cohort Study, CHUV, Lausanne
- Dr. Luigino Dal Maso, Servizio di Epidemiologia e Biostatistica, IRCCS, Centro di Riferimento Oncologico di Aviano, Aviano, Italy

Identification of Multiple Adenoma Susceptibility Genes / The IMAGEN Network (ICP 01358-03-2003)

PD Dr. Karl Heinemann

Forschungsgruppe Humangenetik

Zentrum für Biomedizin DKBW

Universitätskinderhospital beider Basel UKBB

Mattenstrasse 28

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Duration: 1.1.2004 – 1.1.2008

CHF 500,000.–

In collaboration with:

- MD PhD Ian Tomlinson, Molecular and Population, Genetics Laboratory, London Research Institute, Cancer Research UK, London, Great Britain
- Dr. Anne Lyster Knudsen, The Danish Polyposis Register, Hvidovre University Hospital, Hvidovre, Denmark
- Dr. Steffen Bülow, The Danish Polyposis Register, Hvidovre University Hospital, Hvidovre, Denmark

A comprehensive risk-adapted treatment strategy for liver tumours in children and adolescents, consisting of suite of 4 international trials (SIOPEL III–V).

(a) Continuation of SIOPEL III, and (b) a study for recurrent and refractory HB, (c) SIOPEL IV: h

(ICP 01405-08-2003)

Dr. Jack Plaschkes

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Duration: 1.1.2004 – 1.1.2007

CHF 144,700.–

In collaboration with:

- Dr. Rudolf Maibach, SIAK-Koordinationszentrum, Bern
- Dr. Giorgio Perilongo, Dept. of Pediatrics, University Hospital of Padua, Padova, Italy

Towards an independent and efficient anticancer drug development in Switzerland: potentiation of the Swiss SENDO Unit (ICP 01687-03-2005)

PD Dr. Cristiana Sessa

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Duration: 1.1.2006 – 11.2008

CHF 400,500.–

In collaboration with:

- Prof. Franco Cavalli, Istituto Oncologico della Svizzera Italiana (IOSI), Ospedale San Giovanni, Bellinzona
- Prof. Thomas Cerny, Kantonsspital St. Gallen
- Prof. Serge Leyvraz, CHUV, Lausanne
- Dr. Walter Mingrone, Zentrum für Onkologie, Kantonsspital Aarau

International Breast Cancer Study Group (IBCSG)

(ICP 01357-03-2003)

Regula Studer, MSc

International Breast Cancer Study Group (IBCSG)

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INTERNATIONAL EXTRANODAL STUDY GROUP (IELSG) (ICP OCS-01356-03-2003)

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- Prof. Carlo Capella, Ospedale die Circolo Fondazione Macchi, Anatomia e Istologia Patologica, Università dell'Insubria, Dipartimento Scienze Cliniche, Varese, Italy

Further ongoing projects of the CCRP and the ICP

Identification of molecular signatures of human prostate cancer and their validation in animal models an application in the clinics (CCRP 01262-06-2002)

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Duration: 1.9.2003 – 1.9.2006

CHF 1,000,000.–

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- PD Dr. George Thomas, Friedrich Miescher Institut (FMI), Basel
- Dr. Sara Kozma, Friedrich Miescher Institut (FMI), Basel
- Dr. Silke Gillessen, Kantonsspital St. Gallen
- Dr. Pierre-André Diener, Institut für Pathologie, Kantonsspital St. Gallen

Presentation of ongoing research projects

Collaborative Cancer Research Projects (CCRP)

Bertoni Francesco | Primary central nervous system lymphoma: From an improved biology knowledge of its peculiar molecular and biologic feature towards the optimization of treatment

(CCRP 01443-12-2003)

Background

Primary central nervous system lymphoma (PCNSL) is a rare form of extranodal non-Hodgkin's lymphoma that accounts for 4% of all primary brain tumors. Its incidence has been increasing steadily since the 1970s, mainly in immunosuppressed patient populations (due to the spread of HIV and to the greater prevalence of immunosuppressing agents) but also in immunocompetent individuals. The number of patients with PCNSL will likely continue to increase over the next decade.

PCNSL is a very aggressive tumor with a poor outcome, much worse than in lymphomas of the same histotype but arising in other sites. The treatment of PCNSL remains very unsatisfactory: the overall survival is only 20–25% at 5 years. The large majority of PCNSL occurring in immunocompetent patients are diffuse large B cell lymphomas (DLBCL).

To understand the specific issues related to the treatment of PCNSL, we must first understand the underlying unique biology of this tumor. Current biologic knowledge in PCNSL is still largely scarce and several fundamental questions remain unanswered.

Objective

The aim of our project is to obtain more information on the biology underlying PCNSL that will help us to understand its origin and to improve current, suboptimal therapeutic approaches.

Methods

With the financial support we have received from Oncosuisse in a two-year grant, the following objectives are being targeted:

- Set-up of a virtual tissue bank for PCNSL;
- Immunohistochemistry studies to understand the tumor microenvironment;
- Pilot experiments to prove the feasibility of the paraffin expression profiling approach;
- Pilot proof-of-concept experiments for generation of a PCNSL mouse model.

Interim findings

Virtual tissue bank for PCNSL

The availability of material for PCNSL is extremely limited. To overcome this problem, multiinstitutional collaborations are mandatory. Within the International Extranodal Lymphoma Study Group (IELSG), and in collaboration with the International PCNSL Collaborative Group (IPCG), we have set up a virtual tissue bank for residual PCNSL tissue, which can be used for forthcoming biological studies on PCNSL.

The database of the virtual tissue bank is physically located within the IELSG premises at the Oncology Institute of Southern Switzerland, and it is accessible via the IELSG Web site (www.ielsg.org) with any Web browser and any operating system. Pathologists willing to share their archival material receive strictly personal user names and passwords and have to submit only a very limited series of data. Importantly, the actual histological materials remain at the local institutions. Records consist of data anonymously describing pathology and availability of samples. Investigators willing to conduct research on PCNSL can submit a research project to the IELSG; each project will be evaluated for material availability and for scientific relevance.

Immunohistochemistry studies to understand the tumor microenvironment

Parallel to the construction of the virtual tissue bank and the collection of prospective cases, we have also focused on currently available material. A manuscript is in preparation reporting the analysis of 100 immunocompetent patients with PCNSL regarding two aspects of the tumor characteristics, which could represent a prognostic parameter that is easily and routinely assessed at diagnosis on histopathological specimens of PCNSL.

To elucidate the PCNSL environment, we have also been investigating the chemokines that can selectively recruit B and T lymphocytes, as well as NK cells. Dissecting chemokine expression in normal and reactive lymph nodes will improve our knowledge of the process of lymphomagenesis and may lead to a better definition of the homing process involved in the growth of extranodal lymphomas, such as PCNSL.

Pilot experiments to prove the feasibility of the paraffin expression profiling approach

We have been testing different protocols for the extraction of adequate genomic material from archival tissues to assess the feasibility of gene expression profiling from

formalin-fixed paraffin-embedded tissues. These tests have been designed starting from material derived from diffuse large-B-cell lymphomas (DLBCL), due to the scarcity of the PCNSL material. Experiments are still underway. The ability to use RNA and/or DNA from archival material for genome-wide studies would represent a big step forward not only in the context of the current project on PCNSL but also in other settings.

Pilot proof-of-concept experiments for generation of a PCNSL mouse model

We are interested in generating a mouse model for PCNSL. Our working hypothesis is that the gradient of a particular chemokine receptor and its ligand specifies the organotropism of lymphoma cells. To deliver an *in vivo* proof of concept, we have crossbred mice developing B cell lymphomas to transgenic mice ectopically overexpressing the chemokine in an extranodal site. The results of the experiment are not yet available. A model mimicking PCNSL will not only enhance our understanding of the pathogenesis of PCNSL but also be a valuable tool to study potential therapeutic regimens *in vivo*.

Benefit to the patient

The availability of material for Primary Central Nervous System Lymphomas has been extremely limited. Now that any pathologist can submit cases of PCNSL to the virtual tissue bank, biological studies can be conducted in the future. These studies are necessary to improve our knowledge on this lymphoma entity. Additional advantages will hopefully derive from all the other subprojects.

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Brisken Cathrin | The role of Wnt signalling in breast cancer (CCRP 01445–12–2003)

Background

The Wnt signalling cascade has long been shown to be strongly oncogenic in the mouse mammary gland. Despite the clear role of Wnt-1 in inducing mouse mammary tumors, none of the well-characterized signal mediators, such as APC or b-catenin, which are frequently mutated in other human malignancies, are mutated in human breast carcinomas. We hypothesized that Wnt signalling plays an important role in human breast carcinogenesis through novel mechanisms, such as transactivation of ErbB1 and activation of a noncanonical intracellular signalling cascade via RhoA.

Aim of the study

The aim of this study is to combine the skills of three investigators to identify the relevant extracellular Wnt signalling components in the normal breast and during carcinogenesis and to determine which intracellular signalling cascades they activate.

Methods and approaches

We characterize the expression of Wnt signalling components at RNA and protein level in the normal human breast and during breast carcinogenesis using tissue samples, frozen and paraffin embedded, from reduction mammoplasties and breast cancer surgery specimens. The mechanistic basis of the interaction between Wnt signalling and ErbB1 is studied in well-characterized breast cancer cell lines both *in vitro* and *in vivo* xenografts. To study the functional consequences of deregulation of Wnt signalling in the human breast epithelium, we have established primary cultures of human mammary epithelial cells from reduction mammoplasty specimens that we obtain through collaboration with plastic and reconstructive surgeons (Dr. Raffoul and colleagues) at the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne.

Interim findings

We have found that Wnt-1 and Wnt-4 expression are upregulated in human breast carcinomas. Activation of this pathway by means of ectopic expression of Wnt-1 in primary human mammary epithelial cells triggers the DNA damage response and a cascade of events resulting in tumorigenic conversion. The cells cause tumors in mice that resemble medullary carcinomas of the human breast. Notch signalling was upregulated and required for the tumorigenic phenotype. The relevance of these findings for human breast cancer is supported by our observation that established Wnt target genes, such as axin-1 and lef-1 as well as the Notch ligands dll-3 and dll-4 were more highly expressed in a series of human breast tumors than in normal human breast tissue samples. Together these findings suggest that deregulation of Wnt signalling might indeed be an early event in human breast carcinogenesis.

Potential benefit to patients

This project aims at identifying novel predictive markers and therapeutic targets for breast cancer. It should help to determine the role of deregulated Wnt signalling in human breast cancer and to evaluate the usefulness of Wnt signalling components as markers with prognostic and/or predictive value in the diagnosis and treatment of human breast cancer.

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Merlo Adrian | Development of molecular strategies for therapeutic interference with glioblastomas (CCRP 01613-12-2004)

Glioblastoma (GBM) is one of the most aggressive human cancers. Mutations of key molecules within major signaling pathways are frequently associated with tumorigenesis. In a first part of the study, we look at the signaling pathways, specifically at kinases in glioblastomas. Secondly, the role of *Notch2* will be assessed in malignant gliomas, since recent genetic findings point to involvement of this developmental gene in brain tumorigenesis.

Goal of the study

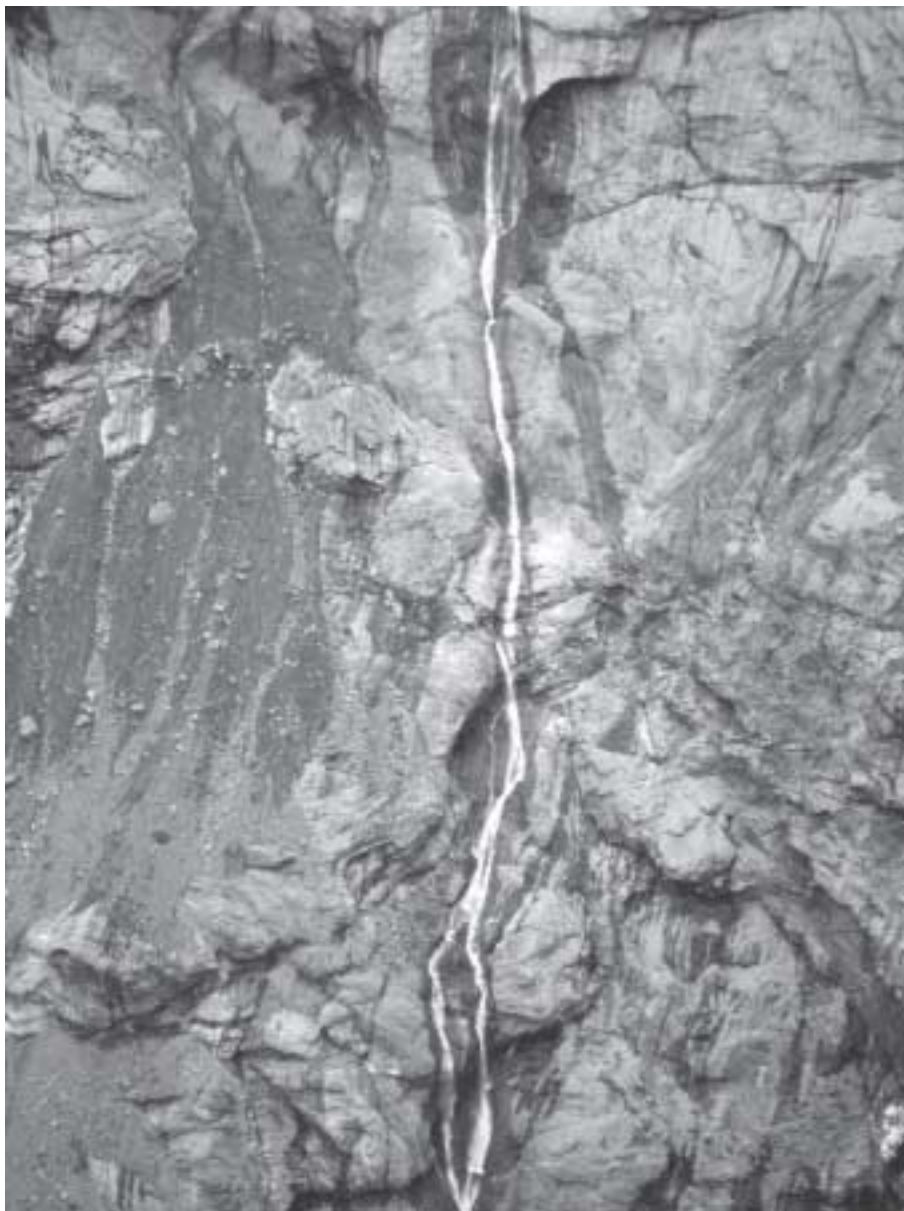
The general objective of this study is to identify the signaling pathways involved in glioblastomas. The focus is aimed at detecting critical cancer genes from the family of genes coding enzymes such as kinases (kinome), which are aberrantly expressed in glioblastomas. The hypothesis that *Notch2* might be an oncogene in glioblastomas will be tested in GBM cells and in a murine tumor model. Furthermore, it will be investigated if this tumor develops from either fully differentiated astrocytes or from neuronal precursor cells.

Methods

To find new kinases as therapeutic targets for GBM, a genome-wide data mining of the expression of the kinome will be performed in glioblastomas, using Affymetrix gene arrays. Phosphorylation status of the differentially regulated signaling pathways will be assessed. Mouse models that either overexpress a kinase or have an inactivated kinase will be generated, so that the functional effects of the enzyme can be established *in vivo*. The effect of Notch2-IC overexpression on neuronal stem cell proliferation as indicated by neurosphere size and on differentiation potential will be investigated. The hypothesis that *Notch2* can act as an oncogene in astrocytomas will be tested in a transgenic mouse model by expressing Notch2-IC under control of the *chicken beta actin* (CAG) promoter in the *rosa26* locus. Secondly the possible role of Notch2 as a tumor suppressor gene in oligodendrogliomas will be tested by crossing floxed Notch2 mice with the same GFAP-Cre deleter strain, to produce a Notch2 knock-out in GFAP-expressing cells.

Interim findings

Initial work so far has involved running Affymetrix gene arrays on the glioblastoma cell lines. Clustering of the differentially expressed kinases having similar expression patterns across the cell lines has generated interesting candidates that will need to be investigated. Furthermore, gene expression of different types of tumor samples consisting of astrocytomas, oligodendrogliomas, and glioblastomas has been measured using Affymetrix gene arrays. Initial experiments have focused on the establishment of the neurosphere culture system and different markers for astroglial, oligodendroglial, and neuronal differentiation have been tested by immunofluorescence microscopy. In addition, a lentiviral vector expressing GFP has been tested for its ability to infect neuronal stem cells and astrocytes. Preliminary results suggest that neuronal stem cells can be transduced by lentiviral constructs. In first experiments, activity of the CAG promoter in the *rosa26* locus in glial cells was confirmed using immunofluorescence microscopy. Different markers, as used in the neurosphere culture system, were tested on mouse brain sections. Furthermore, the construct for targeting the *rosa26* locus was tested *in vitro* in HEK293 cells by cotransfecting a Cre-plasmid to confirm function of the stop cassette. Homozygous floxed Notch2 mice were obtained and will be crossed with GFAP-Cre deleter mice.



Bach 1, 2005, 108 x 144 cm

Benefit to patients

Because of the high degree of interdisciplinarity, this complex work has the potential to identify novel therapeutic targets for glioblastomas. These targets represent the starting point for drug development, provided that the identified targets are found to be frequently altered in *ex vivo* tumor tissue.

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International Clinical Cancer Research Groups (ICP)

Franceschi Silvia | **Risk of cancer in persons infected with HIV** (ICP 01355-03-2003)

Background

Most of the cancers that are exceedingly frequent in people with HIV/AIDS have been shown to be caused by viruses, e.g., Kaposi sarcoma (KS) herpes virus, Epstein Barr virus, human papillomavirus (HPV) and hepatitis B (HBV) and C viruses (HCV). Indeed, HIV is not a carcinogenic virus *per se*, but it enhances cancer risk through disruption of the immune system that, normally, keeps virus-associated cancers at bay.

The introduction of highly active antiretroviral therapy (HAART) in 1996 has decreased progression to AIDS and death among HIV-infected people in Switzerland by over 80%. With respect to cancer risk, however, the immune recovery induced by HAART is decreasing the burden of cancers associated with very severe immunosuppression

(e.g., KS and non-Hodgkin lymphoma, NHL), but, as HIV-infected people will live longer, it may increase the frequency of many other cancers that have a long latent period.

Study aims

- To monitor the impact of HAART on the risk of cancer in HIV-infected people from the Swiss HIV Cohort Study (SHCS).
- To evaluate the interaction between HIV infection/immune impairment and the natural history of cancer-causing viruses such as HPV, HBV, and HCV.
- To envisage strategies (cancer screening, vaccines, smoking cessation) that can prevent cancer development in HIV-infected people.

Methods

The Swiss HIV Cohort Study is an ongoing study that has been enrolling HIV-infected individuals from seven large hospitals in Basel, Bern, Geneva, Lausanne, Lugano, St. Gall, and Zurich as well as through private specialized physicians since 1988. Unique features of the SHCS include not only the large size (over 13,000 people) but also the accuracy of follow-up data, the availability of blood samples, and the possibility to ascertain the occurrence of cancer by means of anonymous linkage with the records of cancer registries in Switzerland. The International Agency of Research on Cancer is conducting other studies on HIV-related malignancies in Europe and in developing countries, thus offering the possibility of international comparisons.

Interim findings

- HIV-infected people who were treated with HAART had a much lower risk of developing KLS and NHL than untreated patients. However, HAART did not show any beneficial effect on the risk of Hodgkin lymphoma and cancers of the uterine cervix, anus, liver, and skin (Clifford, *et al.*, JNCI, 2005).
- Nearly one-third of SHCS patients are also infected by HCV, and 6% are chronic carriers of HBV, thus making future risk of developing liver cancer, and possibly NHL, high.
- In an overview of nearly 6,000 HIV-infected women from all over the world, we found that not only did these women have a much higher prevalence of HPV infection than the general population, but they were also more prone to develop cervical neoplastic lesions from HPV types (Clifford, *et al.*, AIDS, in press) that are rarely dangerous in HIV-negative women (Franceschi and Clifford, JNCI, 2005).

Benefit to patients

As HIV-infected people live longer cancer prevention has become an increasingly high priority. Studies like ours are essential to understand:

- 1) the most important preventable causes of cancer (e.g., smoking, chronic infections with HPV, HCV/HBV, etc.);
- 2) the most effective interventions (e.g., screening, vaccines against HPV, treatment of HBV/HCV, health education, etc.); and
- 3) current barriers to the involvement of HIV-infected people in cancer prevention programs.

A better understanding of the relation between the immune system and cancer risk may ultimately help to prevent cancer also in HIV-negative people.

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Heinimann Karl | **Tumorigenesis in patients with hereditary colorectal cancer – The IMAGEN Network** (ICP 01358-03-2003)

Background

Most colorectal cancers (CRCs) stem from a benign precursor lesion, the polyp (also called adenoma), developing into a carcinoma. About 15–20% of all CRCs are familial in origin, which points to a genetic cancer predisposition. Among these are the familial adenomatous polyposis coli (FAP) and the hereditary non-polyposis colorectal cancer (HNPCC) syndrome, as well as the clinically and genetically heterogeneous group of “familial CRCs,” which account for about 1%, 5%, and 10% of the total CRC burden, respectively. To the latter belong also patients with numerous (also called multiple, <100) adenomas in the large intestine, but in whom, in contrast to most patients with classical FAP, no germ line alterations in the APC gene can be detected (also called attenuated FAP, AFAP). Furthermore, it is unclear how a cell actually becomes a tumor cell: FAP or HNPCC mutation carriers already harbor in all their body cells an alteration (mutation) in one of the two gene copies present; the change into a tumor cell, however, only occurs when the second, normal gene copy is inactivated (this is called the second hit).

Aims

Within the framework of an international collaboration (Basel, Copenhagen, London), the IMAGEN Network (Identification of Multiple Adenoma susceptibility GENes), we aim to investigate a) the underlying genetic cause(s) in patients with multiple adenomas (AFAP) and b) the tumorigenesis (second hit) in FAP and HNPCC mutation carriers.

Methods

The first two years were dedicated to the following tasks:

1. identification and collection of AFAP patients
2. germ line mutation analysis of the APC and/or MYH genes
3. analysis of the second, somatic mutation(s) in tumors from AFAP and HNPCC mutation carriers

Interim findings

In areas 1 and 2 above: Information on 254 AFAP patients was gathered from 12 polyposis registries from 9 countries. Based on a synthesis of the clinical and molecular genetic data, we proposed the following diagnostic criteria for AFAP: a) dominant inheritance and b) presence of 3 to 99 colorectal adenoma in patients 20 years of age and older. Because of milder disease manifestation, therapy and surveillance intervals should be modified accordingly (colonoscopy better than sigmoidoscopy). Among Swiss polyposis patients without detectable APC mutation, 10% were found to carry a germ line alteration in MYH.

In area 3 above: In this brief report, we only report on the results of the AFAP investigation for which 235 tumors (mostly adenomas) from 35 patients (16 families) were screened for somatic mutations: It could be shown that many polyps actually need 3 (and not only 2) additional, somatic hits (mutations) to reach the optimal properties of a tumor cell. This finding may, at least in part, explain the milder phenotype (less polyps and cancer) in certain AFAP patients.

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Plaschkes Jack | **A comprehensive risk-adapted treatment strategy for liver tumors in children and adolescents consisting of a suite of 4 international trials – SIOPEL III to V – a) Continuation of SIOPEL III – b) A study for recurrent and refractory HB – c) SIOPEL IV – d) SIOPEL V (ICP 01405-08-2003)**

SIOPEL III – for both hepatoblastoma (HB) and hepatocellular carcinoma (HCC)

The first part is a randomized trial for standard risk HB (as identified in SIOPEL I), comparing cisplatin only with the standard treatment PLADO (CisPLatin and DOxorubicin). Cisplatin alone was previously tested in a pilot study (SIOPEL II) with good results. The second part is a single-arm study for high-risk HB (Metastatic and stage Pretext IV) using cisplatin doxorubicin and carboplatin. 277 standard-risk HB patients, 196 high-risk HB, and 69 HCC patients have been registered. Accrual for standard-risk children is now reaching the target and results still blinded but will be evaluated in October 2006. The high-risk arm was closed in December 2004, as the results were not significantly better than with PLADO, and replaced by SIOPEL IV.

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SIOPEL IV – for high-risk HB

SIOPEL IV opened in June 2005. The therapy has been further intensified by time and density compression of the same agents, and liver transplantation has been encouraged in selected nonresectable patients. 20 children have so far been registered.

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SIOPEL V

SIOPEL V is a new international trial for HCC in children and young adults up to the age of 30. It is planned as a joint study with adult centers for patients without cirrhosis (hence the age range) that have more similarities to HCC in children. The main strategy consists of primary surgery and the introduction of an antiangiogenic agent (Thalidomide). The aim is to increase resection rates and reduce relapses. The study opened in June 2005 and has registered 7 patients.*

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*The study for refractory and recurrent HB using Irinotecan is continuing until the expected accrual of 25 is reached (17 to date).**

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All the trials mentioned aim to improve the outcome of the main malignant liver tumors occurring in children and adolescents, compared to the previous results from SIOPEL I and II. Also especially in SIOPEL III, the aim is to reduce the toxicity and late effects in standard-risk children that form the majority.

** The accrual in the newer studies has been slow to take off because of the increased and more complicated regulatory measures imposed by the EEC and other bodies.*

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Cristiana Sessa | **Towards an independent and efficient anticancer drug development in Switzerland: potentiation of the Swiss SENDO Unit**
(ICP 01687-03-2005)

Background

The majority of solid tumors are still not curable, and the search for more effective and tolerable therapies is of high priority.

Anticancer drug discovery and development, so far mostly done by the pharmaceutical industry, can be performed more efficiently through the interaction of academia and industry within scientifically independent networks of collaborating institutions.

The Southern Europe New Drugs Organization (SEUDO) is a nonprofit academic group founded in 1998 and located in Milan that coordinates translational studies in Italy, Spain, and Switzerland.

Two Swiss centers have been very active in Switzerland. New centers have expressed their interest to participate to the group. Expertise and resources are available. However, there is a lack of coordination of phase I and early phase II studies.

Aims

The main aim of this project is to set up a Swiss SENDO Unit in order to:

1. establish closer interaction with the institutions and the investigators
2. establish closer interaction with the Swiss Group for Clinical Cancer Research (SACC) to facilitate continuation of the clinical evaluation of new molecules in phase II studies of antitumor efficacy.

Materials and methods

The project foresees the establishment of a Swiss SENDO Coordinating Center in Bellinzona at the Oncology Institute of Southern Switzerland, so far the most active SENDO Institution in Switzerland. The Cantonal Hospital of St. Gall (KSSG) is already an active member, while the Centre pluridisciplinaire d'Oncologie at Centre Hospitalier Universitaire Vaudois (CHUV), the Dept. of Medical Oncology of St. Gall, and Cantonal Hospital of Basel are probationary members. The ICCR will provide financial support for part of the salaries of the research nurse and data manager involved in the SENDO studies and will cover travel costs for participation in educational activities and meetings of the group for the nurses, data managers, and young physicians involved.

Interim findings

Since January 2006 one phase I study testing the toxicity and preliminary antitumor activity of a combination of cytotoxics given orally has been fully implemented in 4 centers; 3 patients are on treatment, and 3 are planned to be enrolled by the end of July.

Two new phase I studies will start by the end of 2006, one with a new camptothecin analog in three centers and the other with a targeted monoclonal antibody in two centers. All of these three studies will be conducted only in Switzerland.

Benefits to patients

The investigators have direct experience with the new compounds, are used to collaborating, and are more motivated to continue working with the same drugs in phase II studies. Better knowledge and direct involvement

of physicians improve the quality of care of patients; it also increases public awareness of the needs and importance of anticancer drug development and, more generally, of clinical research in Switzerland.

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Studer Regula | **International Breast Cancer Study Group (IBCSG)** (ICP 01357-03-2003)

Background

The IBCSG is one of the leading international breast cancer research groups. The research focuses on early stage breast cancer.

Goal of the study

To improve therapy choice, outcome, and quality of life for patients with breast cancer.

Main research areas

Clinical trials: A range of trials for different patient populations is currently coordinated by the IBCSG. These trials are conducted according to the established GSP (Good Clinical Practice) procedures, and include the evaluation of chemotherapy, hormonal therapy, and surgical methods.

Quality-of-life research: Investigates the impact of different therapies on patients' quality of life. Studies on patients' cognitive functions and physician-patient communication are ongoing.

Translational research: The IBCSG maintains a tumor bank and investigates tumor characteristics like receptors, proliferation rate, or tumor markers. The correlation with the clinical outcome leads to more targeted therapeutic strategies.

Interim findings

IBCSG trials yielded important results with impact on patient care. Below, a few recent results:

- In a trial with over 8,000 patients, letrozole has shown higher activity in preventing relapses and a different toxicity profile than tamoxifen. The analysis of centrally reviewed hormone receptors and Her-2 has allowed to further characterize the populations who benefit most from this treatment.
- Another trial has confirmed that trastuzumab is highly effective in reducing the relapse rate in patients with Her-2-positive tumors.
- Quality of life and quality-adjusted survival was evaluated in patients receiving chemotherapy in addition to endocrine therapy. Quality of life improved rapidly after completing chemotherapy, but a benefit was only found in patients with endocrine-responsive cancer.
- The value of tamoxifen after chemotherapy in premenopausal node-positive patients was further clarified: While it is highly effective in preventing relapses for patients with estrogen-receptor-positive tumors, it may have a detrimental effect in estrogen-receptor-negative patients.

These are long-term projects, they started many years ago and patient follow-up is still ongoing. Further evaluations will follow.

Several new trials have been developed and are now open for patient entry. These include:

- Investigation of chemotherapy for elderly patients.
- Tailored treatment investigations for younger patients, studying the role of ovarian function suppression and of aromatase inhibitors (with ovarian function suppression).

Benefit to patients

A woman in the western world has an approximate 10% risk to suffer at one time in her life from breast cancer. Breast cancer is not a uniform disease: more than 20 different types are known, each requiring tailored treatment approaches. Our trials will answer questions how to further improve the therapy of patients, for example: help to define best treatment strategies in younger or elderly patients, establish treatments with better efficacy and less toxicity, and avoid unnecessary or ineffective treatments.

Project coordinator
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Zucca Emanuele | INTERNATIONAL EXTRANODAL 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)

The IELSG was created in 1998 with the precise aim of improving our understanding of extranodal lymphomas. It is centered on the idea that bringing together numerous scientists from different institutions could allow us to amass the data from a sufficient number of patients to study specific extranodal sites of involvement.

The IELSG has already completed and published several clinicopathologic retrospective reviews of extranodal lymphomas, namely, on gastric, intestinal, and testicular large cell lymphomas, on primary CNS and ocular lymphomas, on nongastric MALT lymphomas, and on the mediastinal (thymic) lymphoma. A study on molecular posttreatment monitoring of gastric MALT lymphoma and a molecular pathology study of mediastinal lymphomas have been completed and published as well. Initially, the group consisted of mainly Italian and Swiss centers, but in just a few years it expanded very rapidly to include important institutions and national groups in France, the United Kingdom, Spain, the United States, Canada, and Australia as active members. This success underscores the fact that only a cooperative group can accrue enough cases of extranodal lymphoma to carry out meaningful basic and clinical research. In fact, not only do the different extranodal lymphoma sites have different biologies, but very often different treatment criteria have to be applied, and no single institution will ever be able to accumulate enough cases. Moreover, at least at certain sites, there are still important diagnostic problems, so that a pathology review procedure is absolutely necessary. Therefore, the group has set up a pathologist review panel, and pathologists comprise a large proportion of the IELSG membership.

Starting in 2002, the group decided to launch prospective clinical trials addressing the treatment of specific extranodal disease entities. The IELSG-19, a randomized study of chemotherapy versus chemotherapy plus immunotherapy with antilymphoma monoclonal antibodies in MALT lymphoma, was begun in 2003 and accrued 250 patients in two years. The rapid accrual of a high number of patients with a relatively rare disease provides evidence of the IELSG potential for the improvement of our scientific knowledge and therapeutic results in primary extranodal lymphomas. Other clinical trials are ongoing (for example, a randomized phase II study of high-dose methotrexate versus high-dose methotrexate plus high-dose cytarabine in primary CNS lymphoma and a phase II study of bortezomib in MALT lymphomas). The group was also successful in the challenging undertaking of setting up the IPCG (International PCNSL Collaborative Group) an international collaborative effort to study the primary central nervous system lymphomas (PCNSL) (management of these rare tumors involves many clinical disciplines). The first IPCG achievement was the publication of a consensus paper reporting guidelines to standardize baseline evaluation and response criteria for primary CNS lymphoma.

In November 2004 the IELSG was registered formally as a nonprofit association according to Swiss law. To deal with the administrative problems related to its expanding activity, the IELSG decided to create an IELSG Operation Office for the coordination of the studies at the IOSI (Oncology Institute of Southern Switzerland) in Bellinzona. Detailed data on all the IELSG studies, either closed or ongoing, can be found at the group's Web site: www.ielsg.org

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The three partner organisations at a glance

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Oncosuisse – Swiss Federation Against Cancer

Founded in 1999 as an umbrella group, Oncosuisse is supported jointly by the Swiss Institute of Applied Cancer Research (SIAC), the Swiss Institute for Experimental Cancer Research (ISREC), and the Swiss Cancer League (KLS). Oncosuisse is dedicated to the evidence-based fight against cancer in Switzerland, taking on management and coordinating tasks within cancer research and in the areas of prevention and early detection of cancer, cancer treatment, and coping with the sequelae of cancer (Mission Statement). The foundation Swiss Cancer Research (KFS) raises charitable funds to support Oncosuisse in its activities. The donations are used to promote basic research in oncology; clinical, epidemiological, and psychosocial cancer research; and for further development of the National Cancer Programme Switzerland.

For information, contact

Oncosuisse
Effingerstrasse 40
CH-3008 Bern
Telephone +41 31 389 93 33
www.oncosuisse.ch

Swiss Cancer League (Krebsliga Schweiz)

The Swiss Cancer League is a national, charitable, private organisation. It attends to all aspects of cancer, with the aim to ensure that fewer people develop cancer and more people can be treated successfully. The Swiss Cancer League supports cancer research, increases awareness of prevention measures, is committed to early diagnosis and treatment, accompanies and advises patients and their relatives and offers social support. At the local and regional levels, the 20 cantonal cancer leagues are its main agents. They provide psychosocial counselling and financial support to patients and their relatives locally.

The Swiss Cancer League fulfils its many-sided tasks with the aid of donations. The Swiss Cancer League funds cancer research projects with a special emphasis on supporting patient-oriented research projects.

For information, contact

Swiss Cancer League
Effingerstrasse 40
CH-3008 Bern
Telephone +41 31 389 91 00
www.swisscancer.ch

**Foundation Cancer Research Switzerland
(Stiftung Krebsforschung Schweiz)**

The task of the Foundation Cancer Research Switzerland is fund raising for support of cancer research. The foundation supports cancer research in its full range: from basic research in oncology to clinical research, from epidemiology to psycho-social cancer research. Foundation Cancer Research Switzerland also supports the development and implementation of measures to fight cancer in Switzerland, notably the National Cancer Programme Switzerland.

The large part of funds raised by the foundation is given to Oncosuisse – the Swiss Federation Against Cancer. Oncosuisse awards research grants to projects recommended by the Scientific Committee (WiKo).

For information, contact

Stiftung Krebsforschung Schweiz (KFS)
Effingerstrasse 40
CH-3008 Bern
Telephone +41 31 389 91 61
www.krebsforschung.ch



Blumen der Nacht 11, 2006, 100 x 75 cm

Cancer – current research questions and therapies

Interview with Professor Michel Aguet, MD, director of the Swiss Institute for Experimental Cancer Research (ISREC) in Lausanne

Michel Aguet, what we call cancer is an extremely heterogeneous group of diseases. What do they have in common?

Cancer is definitively caused by genetic damage, damage that is passed on. However, cancer is only in very rare cases hereditary. Cancer usually develops as a result of gene damage that accumulates over a lifetime. That is why cancer is typically a disease that affects older people.

What causes gene damage?

For example, toxic substances, like cigarette smoke or ultraviolet radiation. But also various substances – about which we know too little and which are, for example, contained in foods – can probably cause gene damage.

First, cancer is an anomaly of cell division: the control of cell division is irrevocably destroyed or inactivated, and because of the uncontrolled division process, a cell mass – a tumour – forms. This in itself would not yet be a very serious medical problem. We are familiar with tumours that are benign, such as warts or polyps. In cancer, several other problematic characteristics have to come into play, especially

what we call “anarchic behaviour” – that is, infiltration of healthy tissue and the spread of cancer cells throughout the body – metastatisation. The cancer cells invade healthy tissue and burrow into blood or lymph vessels, and this enables them to spread throughout the body and form metastases.

Does this mean that cancer cells regularly develop in the body but that our immune system is normally strong enough to deal with this?

The repair ability of normal cells is enormous. The DNA repair mechanisms that cells use to repair damage to the genes are very important protective mechanisms. If a cell cannot repair gene damage, it can even initiate deliberate suicide, or programmed cell death. How the immune system recognises a cancer cell and what it does to fight this cell is an important question. Here the opinions differ. Attempts have been made to utilise the immune system for cancer therapy – for example, through vaccinations against cancer. Unfortunately, this branch of research has thus far not yielded any real successes.

Cancerous tissue requires blood vessels so that it can sustain its own metabolism. Does this present an opening for cancer therapies?

It has long been postulated that inhibiting blood vessels is a good starting point for treatment. Over the past 15 years, thanks to some excellent work, the growth factors that are responsible for triggering the growth of blood vessels have been isolated. And it has been found that tumours form those factors to stimulate the growth of blood vessels. The next step in the research was the development of antibodies to inhibit these factors. The antibodies were then tested clinically, and we are now seeing certain effects. The whole thing works best if combined with a traditional chemotherapy. This is undoubtedly a success in the area of therapy.

The tumour is starved, so to speak?

That was the idea when the strategy was developed. In reality, things are more complicated. We are observing that the effect of this therapy is possibly due to effects other than the inhibition of blood vessels. For example, chemotherapy drugs penetrate and are absorbed by the tumour better when the blood vessels in the tumour are damaged.

Have there been other successes in cancer therapies?

Let's remember that we would much prefer, whenever possible, to prevent rather than to treat cancer. Unfortunately, we know the exact cause of cancer in only a few cases, so that prevention is often not possible. But we try to detect cancer as early as possible so that we can intervene in the process at the earliest stage possible. The earlier the disease is detected, the more and the more efficient means we have to tackle it.

Most cancer therapies available today can make too little allowance for the differences between cancer cells and normal cells. That's why very many cancer therapies are so damaging also to normal cells. Re-

search is aiming to identify specific differences between normal cells and cancer cells and to discover the molecular anomalies of cancer cells, so that therapies can target these anomalies directly. Today, *targeted therapies* are being used in clinical practice for the first time – and this as the result in part of about 20 years of research.

Do targeted therapies attack cancer cells specifically? Is healthy tissue immediately adjacent to the cancerous tissue spared?

That is the attempt, at least. To give you an example: in certain cancer cells that divide very quickly and in an uncontrolled manner, there is over-expression of growth factor receptors on the surface. So the main effort is to block/inhibit these receptors. One such substance, trastuzumab (Herceptin®), binds to and blocks these receptors in certain types of breast cancer and thus slows cell division. This is a relatively cancer-specific mechanism: the therapy affects normal cells too, but much less so than in traditional cancer therapies.

Are there ways of interfering with signal transmission within the cell?

Growth signals cause a chain of biochemical reactions that ultimately result in cell division. A whole range of points of attack presents itself here as a foundation for potential treatments. In many cancer cells, these chains of reaction are disrupted; they function spontaneously. They no longer require growth factors and instead constantly emit a "grow" signal. In chronic myeloid leukaemia we have precise knowledge of the particular defect. That's how it was possible to develop a tiny molecule – Glivec® – that brings the previously uncontrolled function under control.

Currently, a whole series of drugs based on this principle of targeted therapy are in the clinical-trial phase. They block either growth factors or the biochemical signal chain. We now understand, however, that the concept of therapy targeting the “Achilles heel” of a cancer cell is too simplistic. In a cancer cell, there exist a number of defects, and it will hardly be possible to inhibit the cells efficiently by inhibiting just one single defect. Many of the new inhibitor substances, however, work on several targets in a cell. But here we are faced with an old problem: drugs that have several points of attack are usually also more toxic, as they also affect normal cells.

Speaking of side effects: Are there ways to tailor chemotherapy for the individual patient?

That is one of the main trends today in the use of cancer therapies. Over the past years, we have learnt that cancer is not one disease but that the term “cancer” encompasses very different diseases. Breast cancer is not one type of cancer but dozens of different cancers, which we can identify relatively well today. Tissue samples show molecular patterns that are specific to individual tumours. It is hoped that we can use this differentiation to predict how a disease will progress and, especially, how it will respond to therapy. That is why tailor-made therapies are certainly a vision for the future. We want to learn precisely what tumours respond to what therapies and what tumours do not, so that patients are not exposed to aggressive treatments unnecessarily.

When a tissue sample is taken from a patient, could you expose the sample to different chemotherapeutic drugs in the laboratory and observe how the cancer tissue reacts to the different drugs? Is this being done?

At the moment, this is still being researched, but that is exactly where we would like to be. We want to be able to predict how a cancer will react to various therapies. But we are not quite there yet. Today, we use so-called markers – for example, the already mentioned growth factor receptors on the cell surface – and then treat only the tumours with the respective markers. By using prognostic markers, we can also distinguish between tumours with varying prognoses. Tumours with a better prognosis are treated less aggressively than tumours that have a worse prognosis. That is where we stand today.

In this connection, it is important to mention that the “old” forms of therapy – surgery, radiation therapy and chemotherapy – are still in demand and still expedient. None of the new therapies has replaced an older one. In future, therapies will be used in combination: for one, in order to reduce the side effects of individual components, and for another, to increase efficiency.

At the beginning of the interview, you said that metastatisation is a big problem. Is research being done in this area as well?

The possibility of inhibiting the metastasising process is of central importance in today’s research. Both the old and the new therapies target mainly the growth of cancer cells. But it is possible that that is not the main problem at all, and that the main problem is metastatisation. And we have hardly any therapeutic options to deal with that. Too little is known about the mutual interactions between cancer cells and healthy cells. Another problem is that cancer tissue is very heterogeneous. Within a tumour there are different kinds of

cells. Even with the new therapies, unfortunately, we observe again and again that the tumour responds to treatment initially, but that the cancer then recurs. Today, we are particularly interested in discovering the characteristics of these recidivating cancer cells. It is thought that in the primary tumour there are certain groups of cells that do not respond to the initial treatment and that these cells are responsible for the recurrence of cancer. These cells are called tumour stem cells. Characterising these subgroups of cancer cells is an important area of research.

Do you think that in future, by combining preventive measures, early detection and different therapeutic approaches, it will be possible to largely cure cancer?

For certain types of cancer, cure will be possible. This is already the case today, for example, for certain types of leukaemia and testicular cancer. In cases where no cure is possible, the hope is that we will be able to control cancer as a chronic disease, like diabetes mellitus, for example. The cancer will continue to exist, but the disease will be better managed, through the combining and adapting of therapies.

Michel Aguet, you are the director of the Swiss Institute for Experimental Cancer Research. Your research area is of direct relevance to clinical practice, where the fight against actual cancers is waged. How are the results of your research being implemented in practice?

Our work consists mainly in gaining an understanding of the molecular anomalies of cancer cells and their abnormal behaviours, with the aim of discovering new foundations for therapies. If we succeed in doing so, then the research attracts the interest of the pharmaceutical industry. Then the job is to develop "blocking" substances. These are developed

partly in collaboration with biotechnology firms, and they then go into clinical trial. That is no longer our area; it is mainly the pharmaceutical companies that test the efficacy of drugs in clinical studies over many years. The process from the discovery of a new target molecule on up to clinical use of a medication usually takes 10 to 15 years. Research being conducted today will therefore have an effect in the form of new therapies only several years from now. But today we can be sure that research has positive outcomes, because research findings generated 10 or 15 years ago are now bearing fruit in the clinic.

*This is a shortened version of an interview with Professor Michel Aguet by Hans Stefan Rüfenacht, science editor at Swiss Radio DRS2, from the radio programme KONTEXT, broadcast on 1 March 2006: "Cancer: Today's perspective and current research projects."
Edited by Eva Ebnöther, Swiss Cancer League.*

Challenges for basic research – The future of the Swiss Institute for Experimental Cancer Research (ISREC)

There have been many times in the past when cancer researchers, having produced new findings and seen encouraging results, believed that they had reached a turning point. But at present, there is no doubt that we are now at an important turning point: it appears that the promise that researching the underlying foundations and molecular anomalies of cancer would produce new targets for therapies and, based on those, new targeted agents is being fulfilled.

Just recently a range of new drugs has become available that could only be developed based on improved understanding of the molecular anomalies in cancer cells: antibodies specific to the antigens found on the surface of various cancer cells, antibodies programmed to act against cell growth factors or growth factor receptors, and synthetic molecules that interfere with the transmission of oncogenic signals – by blocking protein kinases, for example.

But even this breakthrough is accompanied by a sobering insight: the efficacy of these new therapies is rather modest, they are costly, and, often, the predictions developed in scientific studies about the way in which they work in clinical trial turn out to be incorrect. We still have too little impact on the typical progression of cancers: initial responsiveness to therapy, then recurrences, cancer therapy resistance, and finally, all the more aggressive tumour behaviour.

So a great deal more research is needed: further research into the causes of cancer, so that prevention can be improved; early detection, provided that promising treatments are available; the development of new therapy targets; and the discovery of biomarkers that allow researchers to predict progression of the disease and responsiveness to therapy. In basic research, too, certain thematic approaches for future research are gaining momentum: such as research into the tumour environment and the processes that lead to invasiveness and spread.

There are conflicting expectations with regard to basic research. While it is recognised that basic research certainly has the potential for unforeseeable breakthroughs, the expectation is more and more that basic research will generate clinically relevant findings. However, considering the fact that of the forty or more new medications approved in the United States and Europe each year only a very small part are actually innovative agents targeting new target molecules, the contribution of academic basic research to clinical progress should not be overestimated. Most of the new agents that have been approved for clinical use in the past few years (for example, angiogenesis inhibitors or protein kinase inhibitors) were developed by innovative biotechnology companies and then taken over by larger pharmaceutical companies. In today's environment, where the financing of small companies that do not already have highly developed products has become very difficult, it seems that the need for disease-oriented basic research has become even more urgent. The gap between discovery-oriented and application-oriented research, however, remains substantial. Tackling this deficit is an urgent challenge.

It is mainly thanks to technological progress that clinical tumour biology and basic research have come closer to one another in the past few years. In addition to the genome-wide analysis of transcription patterns, there are a number of methods available today for investigating the relevance of biological processes of tumours, which are predominantly studied with models and systems, in human tumour tissue. In future, basic research will probably become increasingly orientated to clinical observations and questions. This scientifically founded convergence will require some structural adaptations in basic research. A favourable trend in this respect is that individual groups of researchers, faced with stagnating or lacking funding, are showing more and more interest in collaborative projects. To support those, of course, additional funds are needed. Precisely to that purpose, the NCCR (National Centre of Competence in Research) in Molecular Oncology, tried to provide incentives. As a result, the NCCR in Molecular Oncology is now supporting several projects that would not

have received funding if they had applied for individual grants, and in some areas they have already generated substantial synergies. ISREC, too, is prepared to face the challenge of closing the gap between basic and clinically-oriented cancer research.

ISREC will be incorporated into the School of Life Sciences at the Swiss Federal Institute of Technology Lausanne (EPFL) in 2008. It will benefit from contact with technology-oriented institutes and from proximity to the departments of chemistry, mathematics, and information technology. This new environment, in which traditionally innovative research at the highest academic level is accompanied by the development of applications, should be beneficial for research of a similar nature in the area of biomedicine. The ISREC foundation, which will continue to exist as an independent organisation, will extend support of the more clinically oriented collaborative research that began with the NCCR. Lausanne is a particularly attractive location for this, with its renowned oncology university hospital and its experimental pathology department, which focuses strongly on molecular oncology.

The Swiss Institute for Experimental Cancer Research (ISREC), in Lausanne

ISREC's mandate is to contribute to the unravelling of the mechanisms of cancer genesis and to thereby provide new paths to therapies and clinical approaches. To achieve this goal, the institute provides researchers conducting research into the molecular causes of cancer genesis with the necessary infrastructure and provides research groups with ideal working conditions. ISREC employs about 200 scientists from 26 different countries. In 2001, ISREC was designated "leading house" of the National Centre of Competence in Research in Molecular Oncology.

The NCCR is a network research programme in molecular cancer research. The programme "particularly aims at establishing new pathways for the translation of progress in basic cancer research into advances in clinical oncology, through an improved interaction between basic researchers and clinical scientists in Switzerland".

Naturally, there are risks involved in moving ISREC to the EPFL. The coherence of the institute and its positioning and attractiveness as a cancer research centre will depend on how it succeeds in this new environment at complementing cancer-oriented basic research with clinic-oriented projects credibly and with high quality – sometimes also with the aim to spark greater interest on the part of industrial partners.



Prof. Dr. med. Michel Aguet
Michel Aguet completed his MD at the University of Zurich in 1974. Up to 1993 Aguet was associate professor at the Institute of Molecular Biology at the University of Zurich. In 1994, he moved to Genentech Inc., San Francisco, to head the Molecular Biology

Department. In 1996 he was appointed director of ISREC, and in 2005 he became affiliated as a full professor in the newly established School of Life Sciences at EPFL.

Further information:

www.isrec.ch
www.nccr-oncology.ch

List of approved research projects

Approved projects in biomedical research in 2004 and 2005 | Total funds allocated CHF 10,214,050.–

Angelillo-Scherrer Anne | KLS 01775-08-2005 | CHF 135,700.–

CHUV, Lausanne

Insights into the role of Gas6 in graft-versus-leukemia effect VERSUS graft-versus-host disease

Beard Peter | OCS 01576-08-2004 | CHF 194,500.–

ISREC, Epalinges

Virus-mediated killing of cancer cells that lack functional p53: an approach to targeting the genetic instability of tumours

Beermann Friedrich | OCS 01500-02-2004 | CHF 243,800.–

ISREC, Epalinges

In vivo screening of candidate genes in melanoma

Carbone Giuseppina | OCS 01513-02-2004 | CHF 174,600.–

IOSI, Laboratory of Experimental Oncology, Bellinzona

Ets-domain transcription factors in prostate cancer

Cerny Andreas | OCS 01479-02-2004 | CHF 106,400.–

Ospedale Regionale di Lugano, Sede Civico, Lugano

Preclinical development of liposomally formulated antivirally active small interfering RNA's (Liforna's) against Hepatitis C Virus as a novel strategy to combat hepatocellular carcinoma

Citi Sandra | OCS 01390-08-2003 | CHF 281,700.–

Department of Molecular Biology, University of Geneva, Geneva

The role of the tight junction protein cingulin in epithelial morphogenesis and differentiation

Dobbelaere Dirk A.E. | OCS 01414-08-2003 | CHF 170,300.–

Institut für Tierpathologie, Molekulare Pathologie, Universität Bern, Bern

A novel role for IKK in centrosome function and cell cycle progression

Donda Alena | OCS 01407-08-2003 | CHF 117,700.–

Biochemistry Institute, University Lausanne, Epalinges

Antibody-CD1d bifunctional molecules for targeting innate immunity to cancer cells

Erb Peter | OCS 01630-02-2005 | CHF 182,000.–

Institut für Medizinische Mikrobiologie, Universität Basel, Basel

Inhibition of the development of basal cell carcinoma by modulating apoptosis via the Gli2 pathway

Frei Christian | OCS 01575-08-2004 | CHF 167,000.–

Zoologisches Institut, University of Zurich, Zurich

The function of Drosophila hypoxia-inducible factor (Hif-1) and its transcriptional targets in cellular growth control

Frese Steffen | OCS 01508-02-2004 | CHF 205,300.–

Department of Clinical Research Laboratory of General Thoracic Surgery, Bern

PG490 (triptolide)-mediated sensitization of non-small cell lung cancer cells to Apo2L/TRAIL-induced apoptosis – in vivo investigation in two different lung cancer mouse models with established tumors

Gönczy Pierre | OCS 01676-02-2005 | CHF 171,100.–

ISREC, Epalinges

Coupling cell polarity and cell division in C. elegans embryos: novel insights into proliferation control mechanisms

Gönczy Pierre | OCS 01495-02-2004 | CHF 291,800.–

ISREC, Epalinges

Cellular and molecular dissection of centrosome duplication in C. elegans: from model organism towards therapeutic opportunities

Grapin-Botton Anne | OCS 01396-08-2003 | CHF 218,800.–

ISREC, Epalinges

Mesenchyme invasion by the pancreas epithelium during normal development: understanding pancreas adenocarcinoma invasivity and metastasis

Greber Urs | OCS 01570-08-2004 | CHF 72,800.–

Zoologisches Institut, Universität Zürich, Zürich

The entry of oncolytic species B adenovirus serotypes into cancer cells

Hajnal Alex | KLS 01504-02-2004 | CHF 271,500.–

Zoologisches Institut, Universität Zürich-Irchel, Zürich

Notch signaling during Caenorhabditis elegans development

Hemmings Brian A. | OCS 01667-02-2005 | CHF 271,350.–

Friedrich Miescher-Institut, Basel

Role of protein kinase B (PKB/Akt) in cell transformation and cancer

Hirth Frank | OCS 01561-08-2004 | CHF 209,200.–

Institute of Zoology, University of Basel, Basel

The role of Brat/TRIM3 in fly and human brain tumor formation

Huard Bertrand | OCS 01391-08-2003 | CHF 156,500.–

Centre médical universitaire, Genève

Use of a spontaneous tumor model to study T cell tolerance to melanoma antigens and test vaccination strategies

Janscak Pavel | OCS 01730-08-2005 | CHF 221,500.–

University of Zurich, Zürich

Study of the role of the human mismatch-repair system in telomere metabolism

Karch François | OCS 01399-08-2003 | CHF 176,500.–

Département de zoologie et biologie animale, Genève

Function of chromatin assembly factor ASF1 in cell cycle control

Krek Wilhelm | OCS 01787-08-2005 | CHF 335,500.–

ETH, Zürich

Roles of F-box protein Skp2-based E3 ubiquitin protein ligases in cell cycle control and neoplastic signalling

Kroschewski Ruth | OCS 01507-02-2004 | CHF 124,000.–

ETH Zürich, Institute of Biochemistry, Zürich

Analysis of Noey2, an unconventional Raf inhibitor

Lingner Joachim | KLS 01675-02-2005 | CHF 187,800.–

ISREC, Epalinges

Evaluation of the telomerase-associated human EST1A protein as a potential target to kill cancer cells

Locher Kaspar | OCS 01558-08-2004 | CHF 169,900.–

Institut für Molekularbiologie und Biophysik, ETH Zürich, Zürich

Mechanistic and structural investigation of human ABC transporters causing multi-drug resistance in cancer cells

Ludewig Burkhard | OCS 01661-02-2005 | CHF 239,500.–

Laborforschungsabteilung, Kantonsspital St. Gallen, St. Gallen

Genetic transduction of dendritic cells with multi-gene murine corona virus vectors and their application in preclinical tumor vaccination studies

Marino Silvia | OCS 01636-02-2005 | CHF 254,500.–

Institut für klinische Pathologie, Universität Zürich, Zürich

The role of Bmi1 in proliferation, differentiation and neoplastic transformation of neural progenitor cells

Martinou Jean-Claude | OCS 01580-08-2004 | CHF 165,800.–

University of Geneva, Geneva

Preventing mitochondrial fission: an approach to block cell division and to decrease tumor growth

McKee Thomas | OCS 01494-02-2004 | CHF 99,300.–

Institut universitaire de pathologie, Lausanne

Generation of B cell lymphomas in mice using a novel herpes virus vector

Michielin Olivier | OCS 01381-08-2003 | CHF 134,600.–
Swiss Institute of Bioinformatics, Epalinges
Rational optimization of peptide vaccines for immunotherapy of cancer

Moelling Karin | OCS 01632-02-2005 | CHF 204,300.–
Institut für Medizinische Virologie (IMV), Universität Zürich, Zürich
Multiple pathway-directed combination therapy against cancer

Moradpour Darius | OCS 01762-08-2005 | CHF 250,700.–
CHUV, Lausanne
Development of a model system to study coinfection by hepatitis B and C viruses – the major causes of hepatocellular carcinoma

Ochsenbein Adrian Franz | OCS 01627-02-2005 | CHF 274,300.–
Klinik und Poliklinik für medizinische Onkologie, Inselspital, Bern
Immunosurveillance of chronic myeloid leukaemia in mice

Odermatt Alex | OCS 01402-08-2003 | CHF 211,700.–
Departement für Klinische Forschung, Inselspital, Kinderklinik, Bern
A novel strategy for controlling steroid hormone-dependent tumors

Orend Gertraud | OCS 01419-08-2003 | CHF 203,700.–
Universität Basel, Biochemisches Institut, 4051 Basel
Role of tenascin-C, syndecan-1 and integrin $\alpha v \beta 3$ on the inhibition of tumor cell adhesion to fibronectin

Peter Matthias | OCS 01727-08-2005 | CHF 236,900.–
ETH Hönggerberg, Zürich
Regulation of genome stability by cullin-based E3-ubiquitin ligases in yeast and mammalian cells

Plückthun Andreas | KLS 01686-02-2005 | CHF 261,500.–
Biochemisches Institut, Universität Zürich, Zürich
Tumor targeting of ERBB2 with designed ankyrin repeat proteins

Radtke Freddy | OCS 01560-08-2004 | CHF 140,600.–
Ludwig Institute for Cancer Research (LICR), Epalinges
The role of Notch2 in murine epidermis

Rüegg Curzio | OCS 01485-02-2004 | CHF 228,200.–
Centre pluridisciplinaire, d'oncologie UNIL et ISREC, Epalinges
Integrin-mediated endothelial cell death: dissection of molecular mechanisms and design of improved Arg-Gly-Asp-based therapeutics

Ruiz i Altaba Ariel | OCS 01584-08-2004 | CHF 312,400.–
Faculty of Medicine, Genève
Role of GLI gene function in brain tumors

Schärer Orlando | OCS 01413-08-2003 | CHF 334,100.–
Institut für Molekulare Krebsforschung, Universität Zürich, Zürich
DNA interstrand crosslink repair in mammals

Simanis Viesturs | OCS 01383-08-2003 | CHF 218,800.–
ISREC, Epalinges
Analysis of the role of centriolin in regulating cytokinesis

Skoda Radek C. | OCS 01742-08-2005 | CHF 339,000.–
Kantonsspital Basel, Basel
The pathogenesis of myeloproliferative disorders

Sommer Lukas | OCS 01726-08-2005 | CHF 171,100.–
ETH Hönggerberg, Zürich
Characterization and functional analysis of cancer stem cells in human neuroblastoma and melanoma

Stamenkovic Ivan | OCS 01656-02-2005 | CHF 173,900.–
Institut Universitaire de Pathologie, CHUV, Lausanne
Analysis of the molecular mechanisms underlying the pathogenesis of EWING'S family tumors

Thome-Miazza Margot | OCS 01379-08-2003 | CHF 171,300.–
Institut de biochimie, Université de Lausanne, Epalinges
The role of Bcl-10 and MALT1 in lymphocyte activation and lymphoma formation

Trueb Beat | OCS 01463-02-2004 | CHF 173,400.–
ITI, Research Institute, University of Bern, Bern
Role of a novel FGF receptor in the formation of tumors

Vorburger Stephan | OCS 01431-08-2003 | CHF 74,600.–
Department of Visceral Surgery and Transplantation, Inselspital, Bern
Systemic gene therapy of hepatocellular carcinoma by tumor-targeted, self-limited E2F-1 overexpression from the human telomerase reverse transcriptase (hTERT) promoter

Walker Paul R. | OCS 01754-08-2005 | CHF 269,200.–
Hôpitaux universitaires de Genève, Genève
Exploration of intracerebral immune responses in a spontaneous astrocytoma model and their exploitation in novel cancer therapies

Ziemiecki Andrew | OCS 01510-02-2004 | CHF 212,700.–
Departement Klinische Forschung, Bern
Transgenic mouse models to study the molecular mechanism(s) leading to the invasive phenotype of mammary tumors

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Scholarships in 2004 and 2005

Durham André-Dante, Ollon | MD-PhD 01715-05-2005 | CHF 150,000.–
The role of Notch2 signaling in murine epidermis (SAMW MD-PhD bursary)
Destination: Swiss Institute for Experimental Cancer Research ISREC, Epalinges

Jandus-Marone Camilla, Lausanne | MD-PhD 01549-05-2004 | CHF 150,000.–
Role of tumor-specific CD4 T-cells in cancer patients (SAMW MD-PhD bursary)
Destination: Ludwig Institute for Cancer Research, Lausanne

Mauti Laetitia, Lausanne | MD-PhD 01716-05-2005 | CHF 150,000.–
Membrane-type matrix metalloproteinases (MT-MMP) in cancer progression (SAMW MD-PhD bursary)
Destination: Experimental Pathology Division, University of Lausanne, Lausanne

Pebernard Stephanie, Epalinges | BIL KLS 01525-02-2004 | CHF 76,526.–
Characterization of the Cds1-Rad60 pathway
Destination: The Scripps Research Institute, La Jolla, California, USA

List of completed research projects in 2004 and 2005

Beard Peter | OCS 01289-08-2002 | CHF 175,900.–
ISREC, Epalinges
Virus-mediated killing of cells that lack p53 activity: an approach to targeting genetic instability in tumour cells

Briskin Cathrin | OCS 01304-02-2003 | CHF 97,900.–
ISREC, Epalinges
A xenograft model for the in vivo study of primary human breast epithelial cells under physiological conditions and during carcinogenesis

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Brunner Thomas | OCS 01161-09-2001 | CHF 263,900.–
Pathologisches Institut, Universität Bern, Bern
Role and mechanism of reverse signaling via death ligands of the Tumor Necrosis Factor family in leukemic T cells

Cerny Andreas | OCS 01479-02-2004 | CHF 106,400.–
Ospedale regionale di Lugano, Lugano
Preclinical development of liposomally formulated antivirally active small interfering RNA's (Liforna's) against Hepatitis C Virus as a novel strategy to combat hepatocellular carcinoma

Constam Daniel | KLS 01101-02-2001 | CHF 230,200.–
ISREC, Epalinges
Analysis of endoderm differentiation in transgenic mouse models

Finke Daniela | OCS 01135-02-2001 | CHF 150,400.–
Departement für Klinische und Biologische Wissenschaften (DKBW), Universität Basel, Basel
Design of adeno-associated virus vectors for mucosal vaccination against pathogens with an oncogenic potential and for gene therapy

Gönczy Pierre | OCS 01100-02-2001 | CHF 294,200.–
ISREC, Epalinges
Cellular and molecular dissection of centrosome duplication in C. elegans embryos: from fundamental mechanisms to anti-proliferative drug discovery

Groettrup Marcus | OCS 01309-02-2003 | CHF 218,100.–
Biotechnologie Institut Thurgau (BITG), Tägerwil
Regulation of CCR7 signal transduction through prostaglandin E2 and its role for dendritic cell migration and tumor vaccination

Gross Nicole | KFS 01086-09-2000 | CHF 206,800.–
CHUV, Département de pédiatrie, Lausanne
Silencing of the CD44 adhesion receptor expression as a mechanism involved in the highly malignant behaviour of human neuroblastoma

Hemmings Brian A. | KFS 01002-02-2000 | CHF 197,000.–
Friedrich Miescher Institut, Basel
Role of protein kinase B (PKB) in cell transformation and cancer

Hemmings Brian A. | KLS 01342-02-2003 | CHF 171,700.–
Friedrich Miescher Institut, Basel
The role of human protein kinase NDR in cell morphogenesis, cell division, growth control and cancer

Hynes Nancy | KLS 01226-02-2002 | CHF 117,500.–
Friedrich Miescher Institut, Basel
A molecular and cellular analysis of breast tumor cell migration: role of the ErbB2 receptor tyrosine kinase in heregulin-induced motility

Imhof Beat A. | OCS 01335-02-2003 | CHF 113,100.–
Centre médical universitaire, Département de pathologie, Genève
The role of junctional adhesion molecule 2 (JAM-2) in tumor angiogenesis



Blumen der Nacht 12, 2006, 100 x 75 cm

Kalberer Christian P. | OCS 01282-08-2002 | CHF 106,900.–

Universitätsspital Basel, Departement Forschung, Basel

Expression of Natural Cytotoxicity Receptors by lentiviral-mediated gene transfer to enhance the potential of natural killer cells in leukemia immunotherapy

Kroschewski Ruth | KFS 01065-09-2000 | CHF 240,000.–

ETHZ, Institut für Biochemie, Zürich

Cell polarity and Cdc42, an analysis for the development of diagnostic markers of human breast cancer

Lingner Joachim | OCS 01275-08-2002 | CHF 167,200.–

ISREC, Epalinges

Evaluation of the telomerase-associated human EST1 protein as a potential target or agent to kill cancer cells

Ludewig Burkhard | OCS 01317-02-2003 | CHF 210,200.–

Kantonsspital St. Gallen, Abteilung Laborforschung, St. Gallen

Genetic transduction of dendritic cells with multi-gene murine corona virus vectors and their application in preclinical tumor vaccination studies

Ochsenbein Adrian Franz | OCS 01312-02-2003 | CHF 169,100.–

Klinik und Poliklinik für medizinische Onkologie, Inselspital, Bern

Improving adoptive T cell therapy in a murine tumor model that expresses the glycoprotein of lymphocytic choriomeningitis virus as model tumor antigen

Radtke Freddy | OCS 01287-08-2002 | CHF 290,300.–

ISREC, Epalinges

Molecular aspects of the tumor suppressor function of Notch1 in the skin and other epithelial tissues

Reymond Alexandre | KFS 01066-09-2000 | CHF 263,300.–

Hôpitaux Universitaires de Genève, Division of Medical Genetics, Genève

Transcriptional Network of the bHLHZip, Max-like gene, M1x

Schmitz M. Lienhard | OCS 01159-09-2001 | CHF 160,100.–

Medizinische Fakultät, Institut für Biochemie, Giessen, Deutschland

Regulation of cell proliferation by homeodomain-interacting protein kinase 2 (HIPK2); Molecular mechanisms and implications for tumor therapy

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Schwaller Jürg | KFS 01077-09-2000 | CHF 172,400.–

Universitätsspital Basel, Departement Forschung, Basel

Understanding the molecular consequences of chromosomal translocations t(1;14) and t(11;18) associated with MALT B-cell lymphoma

Simanis Viesturs | KLS 01219-02-2002 | CHF 161,000.–

ISREC, Epalinges

The role of the cdc14-related phosphatases in controlling cell cycle progression and assuring genome stability

Thome-Miazza Margot | OCS 01168-09-2001 | CHF 226,000.–

Université de Lausanne, Institut de biochimie, Epalinges

The role of Bcl-10 and CARMA-1 in lymphocyte activation and lymphoma formation

Trumpp Andreas | OCS 01113-02-2001 | CHF 166,200.–

ISREC, Epalinges

Combining mouse genetics with liver biology to address whether the c-Myc oncoprotein functions by independently controlling the cell cycle and the cell growth machinery

Walker Paul R. | OCS 01156-09-2001 | CHF 180,800.–

Hôpitaux Universitaires de Genève, Division d'oncologie, Genève

Antigen-specific CD8 T cell responses against brain tumours: the role of brain antigen presenting cells

Wallimann Theo | OCS 01332-02-2003 | CHF 129,500.–

ETHZ, Institut für Zellbiologie, Zürich

Oncogenic alterations of energy metabolism in tumor progression

Zilian Olav | KLS 01125-02-2001 | CHF 167,000.–

ISREC, Epalinges, zurzeit: Helvea S.A., Genève

Functional analysis of Notch-related secreted protein, NRSP, a novel evolutionary conserved LIN/Notch-repeat protein

Presentation of completed research projects

Beard Peter | **Virus-mediated killing of cells that lack p53 activity: An approach to targeting genetic instability in tumor cells** (OCS 01289-08-2002)

Although many current cancer treatments are based on the principle of damaging the cellular DNA using genotoxic drugs or radiation, the reasons why cancer cells are so sensitive to these agents are not well understood. Exposure of cancer cells to DNA-damaging agents can in some cases lead to rapid cell death by cell suicide, known as apoptosis. Frequently, however, especially in the case of epithelial cancers, this is not the case, and the cells, instead of destroying themselves, die when they try to divide. When the damaged daughter chromosomes attempt to separate, they are broken, leading to serious disruption of cellular division, known as mitotic catastrophe.

In our work we use a virus, adeno-associated virus, as a unique tool to discover the responses of normal and cancer cells to DNA damage or DNA replication defects, without harming the cellular DNA itself. This approach also has potential uses in cancer therapeutics.

Mutation of the cellular tumor suppressor protein p53 is a major factor leading to tumor development. The p53 protein has important roles in controlling cell division and cell death after DNA damage. The control of cell death by p53 is not straightforward, however. In some cells p53 can induce cell death in response to damage. But in other cells this same protein is needed to arrest the cell division cycle after irradiation, constituting a cell cycle checkpoint that gives cells a chance to recover and so prevents mitotic catastrophe. Therefore, after genotoxic stress, p53 can either kill cells or rescue them.

Our results have shown that adeno-associated virus induces a DNA damage response in cells, even though it does not harm the cell's own DNA, and that this leads to cell cycle arrest in the G2 phase. Normal cells recover from this arrest and continue dividing, but cancer cells that are deficient in the p53 signalling pathway cannot sustain the arrest and, on entering mitosis still with a persistent DNA damage signal, die.

We have concentrated our research on three aspects: discovering the mechanisms that lie behind the death of cancer cells during cell division; learning what controls the DNA damage signal triggered by adeno-associated virus; and finally making more clear the specificity of adeno-associated virus for certain cancer cells and the role of the damage response in this.

Thus, our research makes use of adeno-associated virus to gain new information about DNA damage signaling and the mechanisms of mitotic cell death in tumor cells. The results will be critical for assessing and developing potential therapies based on the properties of this virus, either alone or to sensitize cells to other agents, or as a basis to identify drugs that act in a similar way.

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Briskén Cathrin | **A xenograft model for the *in vivo* study of how hormones regulate human breast epithelium under physiological conditions and during carcinogenesis** (OCS 01304-02-2003)

Background

The female reproductive hormones control growth and differentiation of the breast epithelium and are closely linked to breast carcinogenesis. They affect interactions among neighboring cells of the same or different type (i.e., epithelial, myoepithelial, stromal, and immune cells). To study this complex crosstalk, my laboratory is using the mouse mammary gland, which can be readily manipulated experimentally. Ultimately, the relevance of our findings to the human situation has to be established. The hormonal control of breast development is generally conserved between mouse and human, but it is unclear to what extent the intercellular and intracellular signaling pathways are shared between the two species. Addressing these issues is especially urgent, since the currently available mouse tumor models poorly mimic human breast cancers, in particular the early stages of the disease.

Aim

Our aim is to develop an *in vivo* model in which human mammary epithelial cells derived from normal or pathological specimens are grown with and without specific hormonal stimulation and in which they will ultimately recapitulate human breast carcinogenesis.

Methods and approaches

Primary human breast cells are isolated from reduction mammoplasty specimens that we obtain in collaboration with Dr. Raffoul and colleagues, Division of Plastic and Reconstructive Surgery, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne. The cells are grafted to the inguinal mammary glands of immunocompromised female mice. The endogenous milk ducts are removed to allow the engrafted human cells to spread and form a new ductal system.

Interim findings

We have compared different immunocompromised mouse strains for their ability to take the human graft and have characterized their mammary gland development. Furthermore, we assessed whether manipulation of the hormonal milieu would improve the take rate.

Potential benefit to patients

This human xenograft model opens up new experimental avenues for breast cancer research that are more relevant to the biology of the disease than currently available *in vitro* or *in vivo* mouse models. The model will allow us to assess the growth properties and signaling pathways of normal, premalignant, and malignant HMECs *in vivo* and enable us to identify differences that can be targeted with drugs.

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Brunner Thomas | **Role and mechanism of reverse signaling via death ligands of the Tumor Necrosis Factor family in leukemic T cells** (OCS 01161-09-2001)

Death ligands of the Tumor Necrosis Factor family, such as Fas ligand, TNFa und TRAIL, play a crucial role in the induction of cell-mediated apoptotic cell death upon interaction with their cognate receptor on target cells. Recent reports suggest that death ligands may also act as receptors and thereby transduce so-called reverse signals. The aim of this study was to characterize the biochemical basis of reverse signaling in leukemic T cells and to identify death ligand-interacting molecules. In addition we aimed at characterizing the role of these molecules in activation-induced degranulation of death ligands. Leukemic T cells were transiently transfected with tagged death ligands and potential death ligand-interacting molecules. Cell surface expression was assessed by flow cytometry, and reverse signals were induced by cross-linking of death ligands with antibodies. Degranulation was induced by cell activation.

Our results demonstrate that in leukemic T cells death ligands are expressed on the cell surface as well as stored intracellularly in granula-like vesicles. Activation of cell surface death ligands did not result in any measurable reverse signals, questioning previously published data. In contrast, activation of transfected cells led to a rapid protein-synthesis-independent but protein-kinase-dependent degranulation of intracellularly stored death ligands. Cell surface Fas ligand was further found to integrate in what are known as "lipid rafts." These cholesterol- and sphingolipid-rich membrane microdomains mediate a concentration and clustering of Fas ligands at the cell surface and thereby enhance their apoptosis-inducing activity.

Our studies demonstrate that posttranscriptional regulation of death ligands by activation-induced degranulation and integration into "lipid rafts" plays a critical role in the control of their apoptosis-inducing activities. Current approaches aim at integrating recombinant death ligands into artificial "lipid rafts" to enhance their apoptosis-inducing activity in tumor cells. Such engineered death ligands may be used for the future treatment of cancer patients.

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Cerny Andreas | **Preclinical development of liposomally formulated antivirally active small interfering RNA's (Liforna's) against Hepatitis C Virus as a novel strategy to combat hepatocellular carcinoma** (OCS 01479-02-2004)

Objective of the study

Hepatocellular carcinoma is increasing in Switzerland. The reason being the increased prevalence of patients with chronic viral hepatitis in advanced stages of the disease, which are at risk to develop liver cell carcinoma. Treatment options for this type of cancer are limited and chemotherapy developed for other types of cancer is of dubious clinical benefit. Surgical removal is possible in early stages as well as liver transplantation, which causes high costs and risks. We were interested to study the use of small interfering RNA molecules to combat hepatitis C virus replication and the development of hepatocellular carcinoma.

Methods and procedures

We evaluated different sequences of the hepatitis C virus as a potential target for the development of small interfering RNA sequences, which were then integrated in liposomes. We studied the *in vivo* pharmacokinetic and pharmacodynamic behaviour of the prototype liposomes in mice and then went on to study them in mice expressing hepatitis C virus in the livers to study the effect of the experimental treatment.

Results and recommendations

The experiments performed allowed us to optimize the encapsulation of small interfering RNA into liposomes and to study their delivery into the liver of mice. Further studies will be necessary to confirm the effect in hepatitis C virus transgenic mice, which will serve as a step on the way to bringing this treatment modality into a clinical application in the future.

Benefit to patients

The study aims to develop a novel treatment approach for hepatocellular carcinoma, which is a cancer that is currently difficult to treat. The study is in a preclinical phase, and potential application will require additional experimentation.

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Constam Daniel | **Analysis of endoderm differentiation in transgenic mouse models**

(KLS 01101-02-2001)

Using the mouse embryo as a model system, we asked how the TGF β -related activity of Nodal is regulated to harness the oncogenic potential of undifferentiated progenitor cells during normal development, especially in the endodermal lineage.

In self-renewing tissues such as the intestinal epithelium, the proliferation of stem cells and differentiation of their descendants must be tightly regulated, since the corruption of terminal differentiation programs, or ectopic expression of embryonic determinants of pluripotency such as the transcription factor Oct4, can initiate tumorigenesis. The aim of this study has been to identify novel molecular mechanisms that stimulate the differentiation of endodermal tissue. In all vertebrates, endoderm appears to be specified by peak levels of a morphogen gradient of the transforming growth factor (TGF) β -related precursor protein Nodal, which are established by Furin, a Nodal convertase coexpressed with Nodal in the mouse node at the "base" of the nascent endoderm germ layer. In addition, studies in *Xenopus* suggested that Nodal signaling in the node may also be stimulated by the mRNA-binding protein Bic-C. Therefore, we wished to determine during what developmental stage Furin is required to promote Nodal signaling, and whether and how Nodal activity in the mouse node is further potentiated by Bic-C. Unexpectedly, targeted expression of a Furin transgene in the node at embryonic day E7.5 was unable to rescue endoderm formation in Furin null mutant embryos (unpublished observation).

Instead, we found that Furin already activates Nodal at the implanted blastocyst stage (E4.5) and thereby maintains undifferentiated progenitor cells marked by the expression of Oct4. Concomitantly, Furin-mediated cleavage also boosts the expression level of Nodal in an autoinductive feedback loop to build up the Nodal signaling threshold that will trigger endoderm differentiation. These results suggest that Furin is required several days earlier than expected to couple the expansion of a pool of progenitor cells and their subsequent allocation to an endodermal fate. A functional analysis of Bic-C also led to unexpected findings. While previous overexpression studies in *Xenopus* suggested that Bic-C might potentiate Nodal signaling to promote endoderm formation, loss-of-function mutations in the mouse show that Bic-C instead controls the function of tubular renal epithelial cells to prevent cyst formation in kidneys.

In ongoing studies, we are investigating why loss of Bic-C results in polycystic disease and kidney failure, and whether it may predispose to kidney cancer.

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Finke Daniela | **Design of adeno-associated virus vectors for mucosal vaccination against pathogens with an oncogenic potential and for gene therapy**

(OCS 01135-02-2001)

Aim of the study

Infections of the female genital tract with papilloma virus frequently lead to cancer disease. In order to protect from an infection with the carcinogenic papilloma virus or other microorganisms, we need the immune system. The aim of the study is to use the defense mechanisms of the immune system to protect mucosal surfaces from infection. Therefore, adeno-associated virus (AAV) can be used as a vaccine to deliver immunogenic fragments of these microorganisms, thus leading to a specific immune recognition and generation of protective immunity. In order to reach this goal, it is necessary to study the viral properties as well as the immunological parameters protecting from cancer disease.

Method

The immune response against a tumor virus was studied in a mouse model. Inbred mice were infected with the mouse mammary tumor virus, and the cellular and humoral immune response was analyzed. The effect of the immune response for the viral load and the frequency of mammary gland tumors was tested. The properties of AAV were tested in vivo and in vitro in cell culture systems. We used a virus expressing what is called a reporter gene. This GFP (green fluorescent protein) reporter gene allowed identification of the cells harboring AAV during acute and chronic infection.

Results

We could show that neutralizing antibodies were capable of blocking amplification of mammary gland infection, chronic infection, mammary cancer development, and transmission of MMTV to the next generation. Systemic neutralizing antibodies could efficiently protect peripheral and mucosal lymphoid tissue from chronic virus infection, even when given after exposure. Our data point out the role of passive immunoprophylaxis after infection with a cancer-inducing pathogen. We could further demonstrate that lentivirus and recombinant adeno-associated virus (AAV) can serve as gene delivery system to introduce a new gene into the host organism. Lentivirus targets dendritic cells, leading to a strong, persistent T-cell-mediated immune response against the recombinant antigen presented by dendritic cells. AAV is capable of transducing epithelial cells and lamina propria cells, making it an excellent candidate to restore a gene defect in the gut.

Benefit to patients

Recombinant viruses are useful tools to mount an immune response against papilloma virus. Immunization with recombinant viruses before and even after exposure to carcinogenic viruses can clear the infection and prevent disease.

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The centrosome is an organelle that allows notably faithful transmission of the genetic information at cell division. Centrosome number must be carefully controlled to ensure faithful chromosome segregation. Normally, a single centrosome is present early in the cell cycle and duplicates once prior to cell division. If the centrosome does not duplicate or, by contrast, duplicates more than once, cell division can yield aneuploid daughter cells that have excess or missing chromosomes. Therefore, it comes as no surprise that cancer cells often exhibit aberrations in centrosome number or structure that correlate with tumor progression. Therefore, excess centrosome duplication could serve as a diagnostic tool to evaluate the progression of certain types of cancer. Moreover, since centrosome duplication occurs only in proliferating cells, proteins that are necessary for this duplication event represent targets of choice for developing antiproliferative agents in the fight against cancer. However, these diagnostic and therapeutic potentials have been underexploited to date, because the mechanisms governing centrosome duplication remain incompletely understood.

We set out to fill the knowledge gap that has prevented capitalizing on these opportunities by studying the cellular and molecular mechanisms driving centrosome duplication using *Caenorhabditis elegans*. Scientists who pioneered the use of this soil nematode as a model system received the Nobel Prize for Physiology or Medicine in 2002. *C. elegans* represents a model of choice for investigating the mechanisms underlying centrosome duplication through a combination of powerful forward genetic, functional genomic, and cell-biological approaches. Along with others, we have identified five proteins required for centrosome duplication in *C. elegans*: ZYG-1, SPD-2, SAS-4, SAS-5, and SAS-6. Of particular interest, we found that SAS-6 is the founding member of an evolutionarily conserved protein family. We discovered that HsSAS-6, the human family member, localizes to centrosomes and that its overexpression results in the formation of excess centrosomes. Furthermore, siRNA-mediated inactivation of HsSAS-6 abrogates centrosome duplication, indicating broad functional conservation among SAS-6-related proteins across metazoan evolution. Three of the other proteins identified in *C. elegans* also have relatives in other species, and thus the mechanisms by which these proteins function are likely to be broadly conserved as well.

As a result from our work, we expect that these five proteins will represent promising targets for developing novel diagnostic and therapeutic tools in the fight against cancer.

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Dendritic cells (DC) are key regulators of the cellular immune response; they carry antigens from a site of infection in the periphery to the draining lymph nodes. The migration of DC to lymph nodes is guided through chemokines like CCL19 (ELC) and CCL21 (SLC). DC upregulate the expression of CCR7, the receptor for these two chemokines, during their maturation and follow their gradient to the lymph node. We recently discovered that human monocyte-derived DC can only migrate towards CCL19 when prostaglandin E2 (PGE2) is present during their maturation *in vitro*. In this project, we have investigated how PGE2 mediates the functional coupling of DC migration to the CCR7 receptor through a detailed investigation of involved signal transduction modules. We could show that in the absence of PGE2, only a weak PKB activation and no intracellular calcium mobilization occurred. Since intracellular calcium chelation interfered with migration, the requirement of PGE2 for calcium mobilization could account for the need of PGE2 for migration.

The requirement of PGE2 is not confined to CCR7-mediated migration but applies also to CXCR4 and C5aR, and it therefore has more general relevance. This function of PGE2, originally demonstrated in monocyte-derived DC, is also valid for the *ex vivo* migration of freshly isolated human myeloid DC. The PGE2 receptors, which mediate this function of PGE2 in humans, have been identified by inhibitor studies as EP2 and EP4. Extensive gene chip experiments have been performed to identify genes that were regulated by PGE2 in human monocyte-derived DC. The function of these genes for the facilitation of CCR7-directed DC migration is now being investigated. These insights are very important for an optimization of DC as cellular tumor vaccines and bear the chance of finding new factors for the pharmacological manipulation of DC migration.

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Neuroblastoma (NB) is a typical childhood neoplasm with an extremely heterogeneous behaviour. Whereas localised and almost benign tumours are diagnosed in young children, the disease is often metastatic and rapidly progressive in patients over 18 months old.

The CD44 receptor is an ubiquitous surface glycoprotein involved in cell adhesion and cell-cell contacts. The CD44 standard protein (CD44H), or its multiple isoforms are differentially expressed on tumour cells. Whereas an en-

hanced expression of CD44H or particular isoforms on cancer cells has been linked to increased metastasis in several cancer types, we have shown that, on the opposite, a loss of functional CD44 was linked to aggressive and metastatic NB tumours, thus supporting the role of CD44 as a tumour suppressor gene.

The identification of regulatory mechanisms controlling CD44 expression on different cancer cells thus appeared essential for a better understanding of the complex and somehow contradictory roles of CD44. In a first step, we addressed two possible causes of CD44 silencing in NB:

- a) The absence of CD44 on NB cells is linked to their neural crest embryonic origin. In this aim, CD44H and isoforms expression was evaluated by immunohistochemical staining of frozen sections of 14–20 weeks gestational age fetal adrenal glands. The CD44 receptor revealed highly expressed on all samples, of all ages, thus ruling out an expression related to this particular stage of the embryonic development.
- b) Loss of CD44 expression may be caused by the hypermethylation (HM) of the CD44 gene regulatory sequences, a well-known epigenetic mechanism of gene silencing. The possible HM of CD44 regulatory sequences was measured on NB patient samples and cell lines. Our results clearly showed that CD44 gene was hypermethylated only in CD44 negative cell lines. In contrast, no CD44 gene HM could be detected on patient tumour samples, irrespectively of their stage or CD44 protein expression. These results thus reveal the likely existence of several regulatory mechanisms of CD44 expression, in different cancer types.

In a second step, the consequences of CD44 silencing on NB aggressive behaviour have been addressed *in vivo*. The measure of *in vivo* orthotopic growth and metastatic dissemination indicate that the aggressive behaviour of NB associated to CD44 silencing can be further enhanced in a specific tumour microenvironment and by the additional expression by cancer cells of the chemokine receptor CXCR4, a molecule already described as involved in directional metastasis.

In conclusion, CD44H expression on NB cells and tumours appears to be controlled by several complex and tumour-specific mechanisms, including gene HM. In addition the aggressive behaviour of the tumour conferred by the loss of functional CD44 expression, is strengthened by the expression of CXCR4 and the tumour microenvironment.

A better comprehension of the complex role of CD44 in the clinical behaviour of NB should allow the development of improved targeted therapies for NB, which dismal prognosis has not evolved in recent years.

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Hemmings Brian | The role of protein kinase B (PKB) in cell transformation and cancer

(KFS 01002-02-2003)

The proto-oncogene protein kinase B (PKB) is implicated in many critical cellular processes, such as differentiation, metabolism, proliferation, and cell survival. Hyperactivation of PKB is a frequent occurrence in several human cancers, and in many cases this hyperactivity is brought about by a deletion or inactivating mutation of the tumor suppressor PTEN, a negative regulator of PKB, or by activating mutations in the p110a subunit of phosphoinositide 3 kinase (PI3K). As a consequence, all PKB-controlled cellular processes are deregulated. Cells with damaged DNA will survive and divide in this context instead of undergoing apoptosis and can accumulate further mutations. Additionally, implication of PKB in angiogenesis and cell cycle control may contribute to cancer induction. Our current work focuses on understanding the mechanisms of PKB activation and the identification of novel general or isoform-specific PKB functions.

Full activation of PKB requires phosphorylation on Thr-308 and Ser-473 by 3-phosphoinositide-dependent kinase-1 (PDK1) and a Ser-473 kinase, respectively. While PDK1 has been well characterized, the identification of the Ser-473 kinase remains controversial. We recently purified two distinct Ser-473 kinase activities. One of them we identified as DNA-dependent protein kinase (DNA-PK), while the other activity could be attributed to the mammalian target of rapamycin (mTOR). By using inducible knockdown systems of DNA-PK and mTOR in cells, we observed that mTOR is the main kinase responsible for Ser473 phosphorylation in growing cells, whereas DNA-PK functions when the cells are subjected to cell stress or following genotoxic insults. Both DNA-PK and mTOR may provide novel drug targets to control PKB activity in cancer cells.

In addition, we identified a novel function of PKB in the control of p53, a critical tumor suppressor protein that is frequently mutated in cancer cells. p53 is a well-characterized transcription factor that responds to DNA damage and other genotoxic stresses by the activation of downstream targets that are involved in repair, differentiation, senescence, growth arrest, and apoptosis. Intracellular levels of p53 are tightly controlled by the ubiquitin ligase Mdm2. Under growth conditions, Mdm2 targets p53 for degradation and thereby maintains low levels of p53 in the cell. We identified two key sites on Mdm2 that are phosphorylated by PKB and enhance Mdm2 protein stability. In a variety of human tumors, aberrant activation of PKB correlates with increased phosphorylation and protein stability of Mdm2 and concomitant inhibition of p53.

Three highly homologous isoforms of PKB (PKBa/Akt1, PKBb/Akt2, and PKBg/Akt3) are expressed in most cell types. To understand the isoform-specific functions of the PKBg isoform in a physiological setting, we generated and analyzed mice deficient in PKBg. We found that in adult PKBg-mutant mice, brain size and weight are dramatically reduced by about 25% due to a reduction in both cell size and cell number. Currently, we are crossing isoform-specific PKB knockout mice with PTEN-deficient mice. Haploinsufficiency of PTEN elicits a wide range of tumors that are, at least in part, due to hyperactivation of PKB. We

want to determine to what extent deficiencies of individual PKB isoforms can attenuate the development of the diverse types of tumors in these PTEN^{+/-} mice.

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Hemmings Brian | **The role of human protein kinase NDR in cell morphogenesis, cell division, growth control, and cancer** (KLS 01342-02-2003)

The human genome encodes 518 protein kinases, and about 70 of those are members of the AGC (protein kinase A, G, and C) class of protein kinases. The NDR family of kinases represents a subclass of the AGC group including the highly related NDR1 and NDR2 kinases. Although the precise function(s) of these kinases is yet to be defined, evidence suggests that both forms of NDR kinase are involved in cancer development. Human NDR1 is up-regulated in progressive ductal carcinoma *in situ* and in some melanoma cell lines. Furthermore, NDR1 can be hyperactivated by S100B, which is overexpressed in over 80 % of metastatic melanoma. NDR2 levels are elevated in a human non-small-cell lung cancer cell line, and NDR2 is potentially up-regulated in B-cell lymphomas in mice.

Our laboratory has shown that human NDR1 and NDR2 are regulated similarly. Both kinases are efficiently activated upon treatment of cells with protein phosphatase 2A inhibitor. Phosphorylation occurs on the activation of segment site Ser281 (Ser282 for NDR2) and the hydrophobic motif site Thr444 (Thr442 for NDR2), whereby both sites are crucial for NDR activity *in vitro* and *in vivo*. We could show that binding of human MOB1 (hMOB1), the closest relative of yeast Mob1 and Mob2, to a conserved N-terminal domain of human NDR1/2 released autoinhibition of activation segment autophosphorylation. Furthermore, the mammalian sterile20-like kinase 3 (MST3) was shown to phosphorylate human NDR1/2 on Thr444/Thr442 *in vitro* and *in vivo*, but not Ser281/Ser282, hence unraveling the nature of the upstream kinase responsible for hydrophobic motif phosphorylation. In parallel, we succeeded in putting the activation of mammalian NDR kinases into a subcellular context. Targeting NDR1/2 itself or its coactivator hMOB1 to the plasma membrane resulted in rapid activation mediated through multisite phosphorylation.

The NDR kinase family also includes the LATS1 (large tumor suppressor 1) and LATS2 kinases that function as tumor suppressors in mammals and invertebrates. Interestingly, we found that human LATS1 is regulated in a similar fashion to human NDR1 and NDR2. Targeting LATS1 to the plasma membrane through hMOB1 leads also to a rapid activation dependent on intact activation segment and hydrophobic motif phosphorylation sites. Overall, our laboratory has established a complex *in vivo* activation mechanism for mammalian NDR kinases involving MST kinases and hMOBs.

To address the physiological function(s) of mammalian NDR, we generated NDR1 knockout mice and are currently developing NDR2-deficient animals. We are also employing RNAi to study the role(s) of human NDR1/2 in tissue culture cells. Data concerning the identification of NDR substrates, NDR's potential role and regulation during cell cycle progression, cell proliferation (considering also conserved mitotic exit network components such as polo-like kinase 1 or Mo25), and consequently NDR's potential function as an oncogene will be addressed in the near future. Overall, further understanding of the mechanism(s) of action of human NDR1/2 may hold therapeutic potential for cancer biology.

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Hynes Nancy | **A molecular and cellular analysis of breast tumor cell migration: role of the ErbB2 receptor tyrosine kinase in heregulin-induced motility** (KLS 01226-02-2002)

Constitutive activation of EGFR and ERBB2 has been implicated in the development of many human cancers. Furthermore, oncogenic ERBB receptors have well-documented roles in metastasis. This prompted our search for novel ERBB2 effector proteins that have roles in tumor cell migration, an important metastatic characteristic. Using a combination of genetics and biochemistry we identified a novel protein, CGI-27 that associated with a P-tyrosine containing peptides in the carboxy-terminal domain of activated ERBB2. Based upon the proven importance of CGI-27 in ERBB-ligand-mediated breast tumor cell migration, we named the protein MEMO, for mediator of ERBB2-dependent motility. We have shown that MEMO has an important role in microtubule outgrowth and cell motility in mammalian cells. Moreover, our results suggest that MEMO is likely to have a broad role in motility since cells stimulated with EGF, FGF or serum showed a reduced ability to migrate when MEMO levels were low.

MEMO is encoded by a gene found in all branches of life. MEMO is a 32 kDa cytoplasmic protein of as yet unknown function. Thus, we are taking various approaches to characterize its biological activity and to test whether MEMO has a role in tumor biology. In order to explore the role of MEMO in metastasis we have used the 4T1 tumor model. The 4T1 cells originally arose from a spontaneous mammary tumor in a Balb/c mouse. Following implantation into the mammary gland, 4T1 cells form primary tumors that rapidly metastasize to the lungs. Using shRNA vectors that stably down-regulate MEMO RNA and protein levels, we have observed that MEMO is required for robust metastatic spread from primary tumors to the lungs. These initial results suggest that MEMO might be a novel target for anti-cancer therapies.



Blumen der Nacht 13, 2006, 100 x 75 cm

Mice with a conditional and a conventional knock-out of *MEMO* have been generated. *MEMO* is essential for embryonic development since *MEMO*^{-/-} embryos die at E13.5. Ongoing experiments should reveal the cause of lethality. Conditional *MEMO* knockout mice are being crossed with transgenic models of cancer. For these studies we have chosen MMTV-polyoma middle T since expression of the transgene induces mammary tumors that metastasize to the lungs. Ongoing experiments should reveal whether *MEMO* has an important role in this well characterized metastatic mammary cancer model.

These initial results suggest that *MEMO* might be an interesting novel target for cancer therapy. Our future studies will be in two directions. First, we would like to know whether or not *MEMO* is aberrantly expressed in primary human tumors. A screen of tumor cells lines did not reveal any anomalies in *MEMO* expression levels in comparison to normal cells. In order to test larger panels of primary tumors we have generated monoclonal antibodies that are being tested for their potential to detect *MEMO* in paraffin sections. Second, we want to position *MEMO* in a signaling pathway and to know if *MEMO* has

enzymatic activity. With this information it should be possible to develop *MEMO* inhibitors that may eventually become useful in cancer therapy.

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Imhof Beat | **The role of junctional adhesion molecule C in tumor angiogenesis** (OCS 01335-02-2003)

For growth and progression, tumors depend on adequate supply of nutrients and oxygen. This is achieved by angiogenesis, the neovascularization of the tumor tissue. During angiogenesis, new blood vessels are formed from the existing vasculature by sprouting of endothelial cells that proliferate and migrate into the avascular tumor, where they form novel vascular tubes. Since angiogenesis

is an absolute prerequisite for tumor growth, blocking this process by novel reagents will prevent further proliferation of tumor cells and thus offer a novel antitumor therapy.

During the process of angiogenesis, individual endothelial cells detach from the vascular tissue and migrate towards a forming tumor in the vicinity. To do so, the endothelial cells have to release the contacts with their neighboring cells and rearrange with other migrating endothelial cells to form sprouts and finally tubes. In a last step these tubes have to be tightened in order to function as a “waterproof” novel blood vessel. Our laboratory recently discovered the adhesion molecule JAM-C, which is involved in the forming of blood vessels and which controls vascular permeability and the emigration of leukocytes during inflammation.

Our anti-JAM-C-antibodies blocked the sprouting of endothelial cells and reduced tumor angiogenesis and growth of experimental tumors. This result is promising and may lead to a novel way of molecular therapy against cancer. Before that, however, we need to understand the molecular mechanisms of JAM-C, and this is in fact complex. Our and other laboratories found that JAM-C interacts with the neighboring endothelial cells by the JAM-B molecule. We then found that JAM-C interacts with higher affinity with JAM-B than with JAM-C. Our antibodies block this interaction, and this could lead to the functional effect of the antibodies. Since tumors and inflammation upregulate mainly JAM-B expression, it would be advisable to use antibodies against JAM-B. We have now produced these antibodies and selected a series that interfere with JAM-B/JAM-C interaction. These reagents will now be used to test whether angiogenesis and tumor growth can be blocked more efficiently than with anti-JAM-C antibodies.

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Kalberer Christian | **Expression of natural cytotoxicity receptors by lentiviral-mediated gene transfer to enhance the potential of natural killer cells in leukemia immunotherapy** (OCS 01282-08-2002)

The treatment of leukemia patients with chemotherapy, irradiation, and hematopoietic stem cell transplantation (HSCT) aims at reducing the tumor load to a minimal level and at replacing malignant blood cells with normal cells of a healthy donor. Nevertheless, therapy-resistant leukemic cells cause disease relapse in a high proportion of patients. Human natural killer (NK) cells are an important part of the innate immune system and are implicated in the surveillance of blood malignancies. Donor-derived NK cells are among the first hematopoietic cells to be generated from transplanted stem cells but often fail to efficiently recognize the leukemic cells. The aim of this research project is to establish novel experimental approaches

using adoptive immunotherapy with NK cells to improve recognition and eradication of residual leukemic cells after HSCT.

We could show that NK cells from acute myeloid leukemia (AML) patients are fully functional in vitro with respect to cytolytic activity and cytokine production and significantly reduce the tumor load of immunodeficient NOD/SCID mice that had been transplanted with autologous AML blasts. This effect may be mediated by highly expressed activating NK cell receptors, since AML blasts recovered from NOD/SCID mice expressed increased levels of the corresponding triggering ligands compared to the injected blasts. To better understand the molecular mechanism of tumor cell recognition by NK cells, genetic modification of NK cells is warranted. To this aim, we established a protocol to routinely transduce primary NK cells with lentiviral vectors. We could show that cellular activation by cytokines rather than active cell cycling determines the infection efficiency. The contribution of single NK cell receptors to NK cell reactivity will be investigated by specific downregulation of gene expression by lentiviral-mediated transfer of small interfering RNAs into NK cells.

Our studies will lead to a better understanding of the role of NK cells in the recognition and elimination of leukemia and will contribute to the development of novel immunotherapies against acute leukemias after stem cell transplantation.

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Kroschewski Ruth | **Cell polarity and Cdc42, an analysis for the development of diagnostic markers of human breast cancer** (KFS 01065-09-2000)

The Rho-GTPase Cdc42 is a key regulator of cell polarity in many diverse cellular systems. Mutations in Cdc42 cause cell transformation, one step in direction to cancer. Cdc42 controls the establishment and maintenance of basolateral polarity of epithelial cells. My results indicated that regulation of the level of GTP bound Cdc42, the active and transforming form of it, is critical for the establishment and maintenance of epithelial morphology. Many cancers arise from epithelia and begin with loss of cell-cell contacts and gain of motility, processes which are equivalent to loss of cell polarity. We speculated that the level of Cdc42-GTP might correlate with cancer progression. Thus, tools to detect the level of Cdc42-GTP could be potentially used as diagnostic tools to detect early stages of epithelial cancer. In addition, as the direct upstream regulators of Cdc42, its guanine nucleotide exchange factors (GEF) are often oncogenes, we sought to identify a Cdc42-GEF relevant in human epithelial cells.

a) We set out to develop a tool to detect the level and localization of Cdc42-GTP. We succeeded in the isolation and characterization of DNA encoding for three recombinant antibodies (scFv) specifically recognizing Cdc42 in its GTP-bound form using D. Neri's phage display library. Pull-down assays demonstrated their *in vitro* and *in vivo* specificity, whereby especially one scFv qualified due to optimal target affinity. The best clone is currently being tested in final experiments. If the results are positive, this fluorescently tagged scFv will be worldwide the best tool to detect *in vivo* the localization of Cdc42-GTP. In addition, if this scFv can be expressed in high quantities, and the correlation between Cdc42-GTP level and cancer state is established, then these antibodies could indeed be used as diagnostic tools.

b) In our biochemical screen for GEFs for Cdc42 specifically from epithelial cells, we identified IQGAP1, a scaffold protein known to interact with Cdc42, E-cadherin complexes, actin, and microtubules and linked to neoplasia. Intense biochemical analysis confirmed that IQGAP1 functions by an unconventional chaperone upstream and downstream of Cdc42. The change between these two functional states is phosphorylation and cell-cell contact dependent. In our attempt to demonstrate its properties also *in vivo*, we identified the molecular mechanism by which IQGAP1 directly activates actin polymerization. Thus, we revealed two properties of IQGAP1 relevant for the development of metastatic cells. First, growth factor-dependent activation of kinases can phosphorylate IQGAP1, leading to the disruption of cell-cell-contacts. And second, activated IQGAP1 activates N-WASP-mediated actin polymerization and migration. Our results therefore complement the emerging mechanisms causing metastasis.

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Lingner Joachim | **Evaluation of the telomerase-associated human EST1A protein as a potential target or agent to kill cancer cells** (OCS 01275-08-2002)

Telomerase is the cellular reverse transcriptase required for the complete replication of chromosome ends, known as telomeres. For this the telomerase reverse transcriptase polypeptide uses as template its tightly associated telomerase RNA moiety, a portion of which is reverse transcribed onto chromosome ends. Because most normal somatic cells lack telomerase, their telomeres shrink with every cell division cycle by approximately 100 bp. This limits their replicative potential, because short telomeres induce an irreversible cell cycle arrest. Indeed, reactivation of telomerase is a key requisite for human cancer cells to attain an immortal phenotype. Inhibition of telomerase activity in tumors may provide powerful anti-cancer treatment.

To explore strategies to inhibit telomerase activity in tumors, we characterized the telomerase-associated hEST1A

protein. This protein is homologous to yeast Est1p, which recruits telomerase to chromosome 3' ends in this organism to enable telomere elongation in S phase. Human EST1A may also be required for telomerase activity *in vivo*, a hypothesis that still needs to be tested. Through transient expression of hEST1A fragments in 293T cells and co-immunoprecipitation experiments, we identified a domain in hEST1A that is required for its association with telomerase. RNase-treatment studies further demonstrated that association of hEST1A and telomerase is mediated by both protein-protein and protein-RNA interactions. Indeed, using purified and recombinant hEST1A, we uncovered that hEST1A binds the telomerase RNA moiety with high affinity.

Identification of telomerase-binding domains should enable us to generate hEST1A mutants that lose the ability to bind telomerase and thus to test whether disruption of the interaction with telomerase inhibits telomere maintenance in cancer cells. This will evaluate the usefulness of hEST1A as a drug target in cancer therapy. We have also characterized the role of the chromosome 3' end-binding protein POT1 in telomerase control and could demonstrate that it inhibits telomerase *in vitro*, prohibiting telomerase access to chromosome end-mimicking substrates. Thus, our results suggest that telomerase activity may be inhibited by stabilizing association of POT1 with telomere ends *in vivo*. Overall, our analysis should provide strategies to inhibit telomerase in cancer cells by targeting telomere and telomerase-associated factors.

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Ludewig Burkhard | **Genetic transduction of dendritic cells with multigene murine coronavirus vectors and their application in preclinical tumor vaccination studies** (OCS 1317-02-2003)

The high incidence of clinically manifest tumors indicates that the immunological surveillance against malignant cells frequently fails. However, both hematopoietic and solid tumors frequently express specific antigens that may serve as targets for immunotherapeutic intervention. Moreover, the detection of tumor antigen-specific "tumor infiltrating lymphocytes" in human malignancies indicates that the immune system may – under certain circumstances – generate efficient antitumor immunity. Protection against tumors depends on a concerted action of a range of immunological processes. Of particular importance is the activation of the cellular immune system with the coordinate expansion and activation of antigen-specific T helper cells and cytotoxic T lymphocytes (CTL).

Strategies to improve tumor immunity should therefore (i) efficiently deliver immunogenic tumor antigens to secondary lymphoid organs and (ii) facilitate presentation of these antigens in an environment that provides optimal

co-stimulatory signals. The ability to manipulate dendritic cells (DCs) by genetically transferring simultaneously several antigens and immunostimulatory molecules represents thus an attractive strategy. Coronavirus-based vectors possess the potential to reach this goal.

The overall aim of this project is the generation of coronavirus-based multigene vectors. During the first two years of this project, we have successfully established a series of coronavirus-based vectors encoding for various (model) tumor antigens and for the immunostimulatory cytokine GM-CSF.

In addition, we have evaluated different strategies for the establishment of packaging cell lines. Taken together, the results obtained during this funding period form the basis for the development of a new class of safe, multigene vectors, based on the human coronavirus 229E, which represents a particularly promising tool to genetically deliver multiple antigens and immunostimulatory cytokines to human DCs.

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Ochsenbein Adrian | **Improving adoptive T-cell therapy in a murine tumor model that expresses the glycoprotein of lymphocyte choriomeningitis virus as model tumor antigen** (OCS 01312-02-2003)

The immune system controls the development of lymphatic and solid tumors in a process called immunosurveillance. It has been shown for different tumor types that infiltration of the tumor by T-cells correlates with an improved prognosis. This indirectly suggests that these T-cells are involved in the control of tumor development. However, if and how the immunosurveillance is influenced by immunotherapies is largely unknown. Adoptive immunotherapy includes the transfer of tumor-specific antibodies or T-cells to patients. Although adoptive immunotherapy is usually quite efficient in preclinical animal models, the therapeutic effect in clinical phase I and II studies is limited to very few patients. In the present project we investigated the effect of adoptive immunotherapy on the endogenous immunosurveillance. This analysis was performed in a very well-defined tumor model in mice. All tumor cells express as model tumor antigen the glycoprotein of lymphocytic choriomeningitis virus (LCMV). This allows analysis of the resulting immune response in detail. The main goal of the studies was to define situations in which adoptive immunotherapy may be successful. These results may be the basis for the selection of patients for clinical immunotherapy studies.

We established melanoma and fibrosarcoma cell lines that express the glykoprotein of LCMV as model tumor antigen on the cell surface. These cells will be recognized by antibodies and by specific T-cells. The tumors efficiently

grew in B-cell- and T-cell-deficient mice. Adoptive immunotherapy with specific cytotoxic T-cells was therapeutically efficient and led to the control of tumor development. In contrast, in immunocompetent mice, tumor development was substantially slower, and transfected fibrosarcoma cells did not grow at all. The analyses of the resulting immune response revealed that the endogenous immune system of the mouse induced antibodies and cytotoxic T-cells against the tumor, which led to the control of tumor development. Surprisingly, adoptive immunotherapy using specific T-cells in immunocompetent mice did not improve tumor control, but in contrast promoted tumor growth. The analysis of the underlying mechanism revealed that the adoptive immunotherapy not only targeted antigen-expressing tumor cells but, in addition, eliminated tumor antigen presenting dendritic cells. These dendritic cells would have been necessary to induce endogenous immune responses and to activate the tumor immunosurveillance. Therefore, the elimination of these dendritic cells results in a reduction or absence of the endogenous antibody and T-cell response.

Our experiments revealed that adoptive immunotherapy may be efficient if the tumor is not controlled by the endogenous immunosurveillance. In contrast, in situations in which the tumor is controlled by the endogenous immunosurveillance, adoptive immunotherapy may crucially reduce the endogenous immune response. In these situations adoptive immunotherapy may not only be inefficient, but probably even harmful.

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Radtke Freddy | **Molecular aspects of the tumor suppressor function of Notch1 in the skin and other epithelial tissues** (OCS 01287-08-2002)

In recent years a substantial body of evidence has accumulated suggesting that the Notch-signaling pathway known to be important during embryonic development plays important roles in regulating self-renewing tissues. In addition, aberrant Notch signaling has been associated with an oncogenic role in tumorigenesis. The best-documented example is acute T lymphoblastic leukemia in humans and mice, which is caused by too much Notch1 signaling. Thus, in the hematopoietic system, Notch1 functions as an oncogene. Although expression of Notch receptor and ligand family members has also been documented for some human carcinomas, their role in the development of epithelial tumors is unclear.

To study the role of Notch1 in epithelial tissues we generated inducible skin-specific gene-targeted mice for the Notch1 gene. Unexpectedly, ablation of the Notch1 gene results first in epidermal and corneal hyperplasia followed by the development of skin tumors and facilitated chemical-induced skin carcinogenesis. In contrast to the common belief that aberrant Notch signaling has exclusively

oncogenic properties, these results clearly show that Notch1 in the murine skin can also function as tumor suppressor.

Aims of our current study

1. Investigation of the molecular mechanisms of the tumor suppressor function of Notch1.
2. Is the tumor suppressor function of Notch1 restricted to the epidermis, or is it instead a general function in epithelial tissues?

Classical biochemical approaches combined with microarray analysis show that loss of Notch1 in the murine epidermis results in decreased expression of the cell cycle regulator CDK1p21, sustained β -catenin mediated wnt signaling in cells that should undergo differentiation, and abnormal sonic hedgehog signaling.

In addition, we investigated the role of Notch1 in the corneal epithelium. Loss of Notch1 in the corneal epithelium leads to corneal hyperplasia, characterized by increased Ki67 staining, vascularization, and expression of epidermis-specific markers, suggesting a cell fate change of the cornea into skin-like epidermis. Analysis of eyelids from Notch1-deficient mice reveals defective Meibomian glands, which are necessary to generate a protective lipid layer on the surface of the cornea. The absence of this lipid layer causes chronic microlesions of the corneal epithelium, which leads to the initiation of a repair mechanism by recruiting corneal stem cells to the wounded area. Wound-healing and transplantation experiments of Notch1-deficient corneas show that Notch1 is essential for the differentiation of corneal stem cells that have been recruited to wounded areas. Notch1-deficient corneal stem cells have lost their ability to differentiate into corneal epithelium and therefore differentiate by default into skin-like epidermis.

Formation of a skin-like epithelium instead of a cornea is also observed in humans suffering from chronic Vitamin A deficiency. The disease is called xerophthalmia. By performing gene-chip analysis we identified Notch1-regulated target genes within the vitamin A metabolism, which uncovers at least partially molecular aspects of our observations.

The finding that Notch signaling can suppress wnt signaling in the skin led us to investigate if this mechanism also applies to other epithelial tissues, such as the intestine, where aberrant wnt signaling is known to be oncogenic. We therefore generated mice in which different key molecules of the Notch-signaling pathway can be inducibly inactivated in the intestine. Postnatal inactivation of CSL/RBP-J, which mediates Notch signaling of all Notch receptors within the crypt compartment, results in the complete loss of proliferating transient amplifying (TA) cells, followed by their conversion into mucus-secreting goblet cells. Our results suggest that Notch signaling is essential for the maintenance of the progenitor/stem cell compartment of the gut.

Since crypt progenitor cells and adenomas (early cancer lesions) have a similar gene expression pattern, the question arises whether proliferating adenoma cells can be differentiated and withdrawn from the cell cycle by inhibiting Notch signaling, similarly to what is observed with crypt progenitors. Indeed, treatment of APC min mice with chemical inhibitors of the Notch-signaling

pathway induces goblet cell differentiation and reduces proliferation in such adenomas, suggesting that specific inhibition of the Notch pathway can drive cells out of cycle despite the fact that Wnt signaling remains active. This 'proof of principle' experiment highlights the Notch pathway as a potential drug target for the treatment of intestinal neoplasia.

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Reymond Alexandre | **Transcriptional network of the bHLHZip Max-like gene, Mlx** (KFS 01066-09-2000)

Two parallel networks of proteins

The transcriptional regulatory proteins of the Myc proto-oncogene family have been linked to multiple aspects of eukaryotic cell function, including cell cycle progression, growth, differentiation, and apoptosis. All the members of this protein family interact with another protein of the same family called Max, a prerequisite for DNA binding. These complexes elicit different transcriptional responses. Some will activate genes involved in cellular proliferation, while others will inhibit their expression, thus promoting cellular differentiation. We had identified a Max-like protein, Mlx, able to dimerize with some of the proteins known to dimerize with Max. These results suggested that Mlx might act in a regulatory pathway parallel to the Max-driven network of proteins. To confirm this hypothesis, we looked for unknown members of this pathway and then assayed if they could promote or inhibit cell proliferation. We identified a new protein WBSCR14 that could bind DNA upon interaction with Mlx. We subsequently showed that this complex of proteins was able to suppress proliferation, suggesting that indeed the Mlx pathway was functioning parallel to the Max pathway. Interestingly, we found that the gene encoding WBSCR14 was situated in a chromosomal region deleted in the Williams-Beuren syndrome, thus suggesting that this gene may contribute to some aspects of this pathology.

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Schmitz M. Lienhard | **Regulation of cell proliferation by homeodomain-interacting protein kinase 2 (HIPK2): Molecular mechanisms and implications for tumor therapy** (OCS 01159-09-2001)

The serine/threonine kinase HIPK2 is a critical regulator of the p53 tumor suppressor. The p53 protein is mutated in approximately 50% of human tumors and plays a pivotal role for the maintenance of genomic stability. DNA damage results in the activation of HIPK2, which in turn phosphorylates p53 at serine 46 and thus contributes to the induction of apoptosis. HIPK2 was also identified as a regulatory component of the Wnt-signaling pathway that is frequently affected in tumors of the gastrointestinal tract.

The goal of this project is to achieve a better understanding of the molecular mechanisms regulating the activity of the antiproliferative kinase HIPK2. Recent results from other labs show aberrant expression levels of HIPK2 in breast and thyroid carcinomas.

Biochemical- and molecular-biology-based approaches are used.

We investigated the molecular mechanisms that lead to the activation of HIPK2. We found that the antiproliferative and p53 phosphorylating functions of HIPK2 depend on the presence of the PML protein. At the beginning of apoptosis, caspase-mediated cleavage of the C-terminal HIPK2 part leads to the removal of an autoinhibitory domain and the generation of hyperactive HIPK2 fragments. This allows the rapid amplification of the p53-dependent apoptotic program during the initiation phase of apoptosis by a regulatory feed-forward loop. The active HIPK2 fragments are further degraded during the execution and termination phase of apoptosis, thus ensuring the occurrence of HIPK2 signaling only during the early phases of apoptosis induction.

The benefit to patients is a better understanding of the signaling pathways governing the activity of this antiproliferative enzyme.

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Schwaller Jürg | **Understanding the molecular consequences of chromosomal translocations t(1;14) and t(11;18) associated with MALT B-cell lymphoma** (KFS 01077-09-2000)

Background

Both chromosomal translocations t(11;18)(q21;q21) and t(14;18)(q32;q21) occur exclusively in mucosa-associated lymphoid tissue (MALT) B-cell non-Hodgkin lymphoma and lead to formation of an API2-MALT1 fusion or IgH-mediated overexpression of MALT1.

Aim

The goal of our study was to experimentally address the role of these proteins in nuclear factor kappa B (NF- κ B) signaling, a major signaling pathway in the pathogenesis of hematological cancers.

Methods

Using retroviral gene transfer, we expressed MALT1 and apoptosis inhibitor-2 API2/MALT1 in human B-cell lymphoma cells and analyzed the effect on NF- κ B signaling.

Results

MALT1 and the API2-MALT1 fusion were found to be concentrated in membrane lipid rafts along with endogenous MALT1 and 2 binding partners involved in NF- κ B signaling, B-cell lymphoma 10 (BCL10) and CARMA1 (caspase recruitment domain [CARD]-containing membrane-associated guanylate kinase [MAGUK] 1). Both, API2-MALT1 and exogenously expressed MALT1, increased constitutive NF- κ B activity and enhanced I κ B kinase (IKK) activation induced by the CD40 stimulation. Both transgenes protected BJAB lymphoma cells from FAS (CD95)-induced cell death, consistent with increases in NF- κ B cytoprotective target gene expression, and increased their proliferation rate. Expression of a dominant-negative I κ B mutant showed that these survival and proliferative advantages are dependent on elevated constitutive NF- κ B activity. This finding is furthermore supported by increased expression of cytoprotective NF- κ B target genes such as BclXL and API2. Our findings support a model in which NF- κ B signaling, once activated in a CD40-dependent T-cell-mediated immune response, is maintained and enhanced through deregulation of MALT1 or formation of an API2-MALT1 fusion.

Significance/Conclusion

Our study demonstrates that a consequence of two different MALT-associated translocations is deregulation of a signaling pathway involving MALT1, BCL10, and CARMA1, leading to increased constitutive NF- κ B activation, providing growth and survival advantage to the tumor cells. Recent consecutive studies have provided evidence that deregulation of this pathway is not limited to MALT but is also a key event in the pathogenesis in high-grade B-cell lymphoma. These results suggest that interference with the MALT1/BCL10/CARMA1 signaling pathway may provide a new avenue for targeted therapy for malignant B-cell lymphoma.

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Blumen der Nacht 10, 2006, 100 x 75 cm

Simanis Viesturs | **The role of the Cdc14p-related phosphatases in controlling cell cycle progression and assuring genome stability** (KLS 01219-02-2002)

Cdc14p-related phosphatases have been conserved through evolution and have been implicated in regulation of many events in the cell division cycle. We used the fission yeast model to investigate the role and regulation of flp1p, the *S. pombe* orthologue of Cdc14p. As localization is an important mode of regulation of these proteins, we identified domains of flp1p that are required for its localization and function. Mutants lacking *flp1* function show an increased rate of chromosome loss during division, leading us to analyze proteins implicated in regulation of intermitotic events.

Flp1p is sequestered in the nucleolus during interphase, where it is thought to be inactive. During mitosis, it associates with centromeres, the mitotic spindle, and the contractile ring. Flp1p can be divided into three domains, called A, B, and C. B contains the sequence motifs required for phosphatase activity. A has little sequence homology to B but folds similarly. Together, these domains form what is called the DSP fold, which interacts with substrates. The A and B domains, which represent

the N-terminal two thirds of the protein, are well conserved through evolution. The C domain is less well conserved and has not yet been crystallized.

To perform a domain analysis of flp1p, the gene was first tagged at its N or C terminus with GFP to allow localization and also to check for expression. Truncations were integrated into the genome. The localization of the protein was assessed by microscopy, and the biological function was tested by introducing it into genetic backgrounds where *flp1* function is essential for survival.

We found that the A and B domains are required for biological activity, while the C domain is not. Analysis of truncated proteins expressed in *flp1* null cells showed that the C domain remains in the nucleolus throughout the cell cycle. A mutant protein consisting of only the A and B domains was found throughout the nucleus in interphase and localized normally in mitosis. Thus, the C domain is required for nucleolar retention, while A and B are important for mitosis-specific localization. Expression of the C domain in wild-type cells revealed that it localized

like the wild-type protein. This suggested to us that flp1p might interact with itself, which was confirmed by co-immunoprecipitation of two flp1 proteins carrying different epitope tags. We conclude that flp1 proteins can interact in trans *in vivo* and can form multimers *in vitro*, suggesting that autoregulatory mechanisms may contribute to controlling flp1p.

Analysis of mitotic regulators indicated that the localization of the aurora family kinase and microtubule associated protein pcs1p were both abnormal. This may contribute to the decreased fidelity of chromosome transmission that we have observed in flp1-mutant cells.

The insights gained into the function of these conserved proteins may shed light upon how genome stability is assured in human cells.

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Thome-Miazza Margot | The role of Bcl-10 and Carma1 in lymphocyte activation and lymphoma formation (OCS 01168-09-2001)

Short summary of the study

The subject of this study is the molecular characterization of the protein Bcl-10 (B-cell lymphoma-10) and its binding partner Carma1, which play a key role in the activation and proliferation of lymphocytes and whose expression or function is deregulated in MALT (mucosa-associated lymphoid tissue) lymphomas and in activated B-cell (ABC)-type DLBCL (diffuse large B-cell lymphomas).

Goal of this study

MALT lymphomas arise from chronic inflammation caused by infection (for example, with *Helicobacter pylori*) and can be cured in the majority of cases by elimination of the pathogen. However, 20–30% of these lymphomas are resistant to antibiotic treatment. These cases show chromosomal translocations that affect the expression and function of Bcl-10 (5%) or the Bcl-10-binding protein Malt1 (30–50%) and lead to constitutive activity of these proteins. Through the biochemical analysis of the molecular function of Bcl-10 and its interaction partners, we hope to shed light on the principles underlying their dysfunction in B-cell lymphomas.

Methods and approaches

We use cell lines derived from lymphoid malignancies to characterize the molecular function of Bcl-10 and its interaction partners in the control of lymphocyte activation and proliferation. This system allows us, for example, to address the effect of point or deletion mutants or of altered expression levels of these proteins on cellular survival and on antigen receptor-induced cellular activation. Moreover, the cell lines can be grown in sufficiently large quantities that allow us to apply biochemical approaches to identify posttranslational modifications of these proteins and to isolate binding partners, and thus to generate information that is crucial to the understanding of the malignancy-promoting effects of these proteins.

Results achieved

Through combined bioinformatics and molecular biology approaches, we have identified Carma1 as a protein that associates with Bcl-10. Moreover, we could show that a mutation or deletion of Carma1 impairs the capacity of the antigen receptor to induce NF- κ B activation and lymphocyte proliferation. The relevance of these findings is underlined by the recent independent publication of Carma1 and Bcl-10 as proteins that promote malignancy of ABC-DLBCL, a particular form of B-cell lymphoma that critically depends on constitutive NF- κ B activity. More recently, we have identified a novel, NF- κ B-independent function of Bcl-10 in the regulation of the actin cytoskeleton. Whether this function of Bcl-10 is relevant to B-cell transformation is the focus of ongoing studies.

Benefit to patients

The elucidation of the molecular functions of Bcl-10 and Carma1 identifies new drug targets and thereby allows the development of novel therapies that treat antibiotic-resistant MALT lymphomas and certain forms of DLBCL more specifically. By interfering with the function of key tumor-associated molecules, such drugs are expected to show high efficiency and minimal side effects, which would be an essential benefit for patients.

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Trumpp Andreas | Combining mouse genetics with liver biology to address whether the c-Myc oncoprotein functions by independently controlling the cell cycle and the cell growth machinery (OCS 1113-02-2001)

Background

c-myc is one of the most frequently mutated oncogenes found in human tumors. It encodes a transcription factor that controls a series of other genes and is overexpressed in more than a third of all tumors. The *c-myc* gene is required for normal development of the embryo and plays an important role in various organs. When *c-myc* is overexpressed in tumors, it leads to the deregulation of various cellular processes, including cellular growth, cell cycle progression, apoptosis, and stem/progenitor differentiation.

Aim

The biological processes controlled by *c-myc* in the adult organism remains largely unknown. To address this question we generated specific mouse mutants in which mice lack *c-myc* in the liver. The liver is the only organ that has the potential to regenerate after partial hepatectomy. In addition, toxic insults cause pathological hepatomegaly. Our aim is to determine the role of *c-myc* in the control of these proliferative events and why *c-myc* overexpression leads to liver cancer.

Methods

To examine the role of *c-myc* we deleted this gene in the adult liver and challenged the animals using three protocols: fasting/refeeding, liver regeneration, and liver proliferation in response to the xenobiotic TCPOBOP. In addition we used DNA microarrays to monitor the expression of 35,000 genes in each situation.

Results

Our studies identified *c-myc* as one of the primary factors that are required for liver regeneration. Using microarray analysis we identified a number of novel proteins potentially involved in the regeneration process. In addition, we showed that liver proliferation induced by the xenobiotic inducer TCPOBOP is also *c-myc* dependent. We further demonstrated that *c-myc* is a target of the constitutive androstane receptor CAR and a critical component mediating the proliferative response to TCPOBOP/CAR signaling. Finally, our microarray studies identified the transcription factor FoxM1 as a novel gene target of *c-myc* that mediates the proliferative activity of this oncogene during liver hyperplasia.

Significance for the cancer patient

By exploring the oncoprotein *c-myc* we have identified FoxM1 as a novel factor that mediates the proliferation of hepatocytes and is most likely also involved in *myc*-dependent development of liver cancer. If this can be confirmed, development of specific FoxM1 inhibitors could serve as putative novel factors to inhibit the growth of liver cancers.

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Walker Paul R. | **Antigen-specific CD8 T cell responses against brain tumors: the role of brain-antigen-presenting cells** (OCS 01156-09-2001)

Brief outline of the study

Antigen-presenting cells (APCs) have a central role in tumor immunity, because they activate and regulate tumor-specific T lymphocytes that can mediate tumor rejection in experimental cancer immunotherapies. In this project we investigated how brain APCs interact with tumor-specific T lymphocytes *in vitro* and *in vivo*.

Objectives

1. What is the role of brain APCs in immune responses against brain tumors?
2. Can brain APCs be identified, isolated, or cultured?
3. How can we exploit brain APCs for cancer therapy?

Methods

In vitro studies. Isolation of putative brain APCs from mouse brain and coculture with tumor-specific T lymphocytes.

In vivo studies. First model: a glioma with a deficiency in presenting a model tumor antigen was implanted in mouse brain to determine the importance of endogenous brain APCs. Second model: tumors were implanted in different sites, then the phenotype of tumor-specific T lymphocytes was analyzed after activation by APCs migrating from the tumor site.

Results

Cytotoxic T lymphocytes were efficiently activated and subsequently recruited to brain tumors only when brain APCs capable of presenting tumor antigen were present in the mouse. *In vitro* studies suggested that brain-derived microglial cells and macrophages were not capable of taking up tumor antigen and presenting peptides to cytotoxic T lymphocytes. This function was limited to dendritic cells (DC) that could phagocytose tumor antigen *in vivo*, migrate to cervical and lumbar lymph nodes and then prime and imprint T lymphocytes with a unique pattern of adhesion molecules that facilitated homing of activated T lymphocytes back to the tumor in the brain. Critically for future immunotherapies, T lymphocyte priming with optimal (brain-derived) DC induced almost 3-fold better recruitment of cytotoxic T lymphocytes to the brain than T lymphocyte priming with DC that had captured antigen from a subcutaneous tumor.

Benefit to patients

Our results have unraveled some of the mechanisms by which cytotoxic T lymphocytes can efficiently traffic to tumors in different sites, essential for efficacious regional tumor immunity. To incorporate these findings in future treatments, we must identify the signals that are received by APC capturing tumor antigen at the tumor site. We can then envisage that future vaccines may be able to prime tumor specific T lymphocytes and direct them to tumors growing in a given tissue.

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Wallimann Theo | **Oncogenic alterations of energy metabolism in tumor progression** (OCS 01332-02-2003)

Cancer and cellular energetics

Cancer research has been very successful in identifying many of the primary events that lead to cell transformation and eventually to tumor development and progression. However, to grow, invade, and develop its malignant potential, an oncogenic reprogramming of cancer cell metabolism seems to be necessary. Metabolic adaptations like resistance to hypoxia or hypoglycemia and increased rates of glucose uptake and aerobic glycolysis confer a selective advantage to malignant over normal cells, thus promoting tumor progression. Although strategies designed to prevent such adaptations could be particularly effective in cancer therapy, the underlying mechanisms are poorly understood.

Specific kinases involved in cellular energy homeostasis play a key role in such adaptational processes. Many of these kinases occur in the form of different isoenzymes, some of which are already known to show altered expression levels in certain tumors. For example, hetero-trimeric AMP-activated protein kinase (AMPK) isoenzymes are part of a protein kinase cascade that is activated by a drop in cellular ATP/AMP ratios, thus acting as a cellular energy sensor. Once activated, AMPK inhibits ATP-consuming metabolic pathways and compensates ATP depletion by activating ATP supply. In particular, AMPK increases glucose uptake and glycolytic rate, interferes with cell cycle control, and inhibits certain apoptotic pathways. All these effects are known to promote malignant cell progression. Creatine kinase (CK) isoenzymes catalyze the reversible transfer of a phosphoryl group from ATP to phosphocreatine (PCr). This creates a temporal and spatial cellular energy buffer that may protect cancer cells against energy deficits, hypoxia, and apoptosis.

In this project, we evaluated the potential role of these and related kinases, including the tumor suppressor LKB1 kinase, in cancer progression. A molecular characterization of CK, AMPK, and LKB as a first step towards new diagnostic tools and identification of new drug targets was achieved, and the atomic structure of BB-CK and of mitochondrial CK – both “energy enzymes” involved in the energetics of cancer – have been solved. We developed antibodies as important scientific and diagnostic tools and initiated a large-scale screening of tissue microarrays for overexpressed and/or activated kinase isoenzymes. Furthermore, we could show that anthracyclines, belonging to the most potent of anticancer drugs but also showing potentially severe side effects on the heart, act directly on CK and AMPK, thus explaining some of the cardiotoxic effects of these drugs.

Our projects are likely to yield (i) scientific knowledge on the mechanisms of tumor progression, (ii) diagnostic tools to analyze progression state and/or clinical outcome, and finally (iii) proposals for new drug targets and, by their molecular structure, allowing for rational drug design. Finally, strategies can now be developed to alleviate the cardiotoxic side effects of the potent anthracycline anti-cancer drugs.

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Zilian Olav | Functional analysis of Notch-related secreted protein, NRSP, a novel evolutionary conserved LIN/Notch-repeat protein

(KLS 01125-02-2001)

We identified Stealth *in silico* as a new distantly Notch-related protein family. In the animal kingdom, Stealth is strongly conserved across evolution from social amoebas to simple and complex multicellular organisms, such as Dictyostelium, hydra, and human. In bacteria, Stealth is encoded by subsets of strains mainly colonizing multicellular organisms. Some bacterial Stealth proteins transfer hexose-1-phosphate moieties for building up extracellular polysaccharides in some mostly pathogenic and commensal prokaryotes that colonize multicellular hosts. Even though these polysaccharides turned out to be dispensable for free living Stealth bacteria, they were shown to be essential for unicellular organisms to escape innate immune defense during colonization of hosts. Hence, we targeted Stealth in mice to analyze the protein for its role in development and immunity of mammals.

Absence of Stealth during mouse development led to cerebellar defects and perinatal lethality, or, in a different genetic background, allowed mutant mice to survive. Mutant strains are currently being investigated for the role of Stealth in (1) the innate immune system, and in (2) the regulatory cross-talk between innate and adaptive immune defense during microbial colonization. Thus, the immune system of these mice will be challenged with bacterial and protozoan pathogens and immunological agents. Insights into Stealth's potential function in immunity are expected to indicate if (3) Stealth overexpressed by malignant cells contributes to their escape from immune surveillance during tumor growth. Moreover, mutant mice are also being analyzed for Stealth's role in (4) the development of the cerebellum. Analysis of mutant brains for morphological and molecular defects shall be followed by functional *in vitro* assays of respective cell explants.

Meanwhile, the mammalian Stealth gene has not only been shown independently by others to encode the lysosomal α / β -precursor of *N*-acetylglucosamine-1-phosphotransferase, confirming our hypothesis of Stealth being a hexose-1-phosphoryl transferase in man, but has also proved to cause mucopolysaccharidosis II when deficient.

Deciphering Stealth functions might indicate to us how the patient's immune system could be fostered for fighting against foreign organisms while leaving the body's own structures intact. Further, it remains to be shown if drugs selectively inhibiting Stealth in pathogens will help fight Stealth-mediated infections. Moreover, there is good reason to speculate that acquisition and spread of Stealth in pathogens could be responsible for future epidemic outbreaks of infectious diseases.

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Further research projects completed in 2004 and 2005

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Oligonucleotide-based transcriptional repressors for cancer therapy

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The role of JAM-2 in human brain tumors

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Mechanisms of B lymphoma cell elimination following anti-cd20 antibody (rituximab) treatment

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The role of Bmi1 in cerebellar development and in medulloblastoma pathogenesis

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Molecular mechanisms of tissue remodelling in cancer progression

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The role of Rheb (Ras homologue enriched in brain) in the mTOR signaling Pathway and its involvement in the pathogenesis of tuberous sclerosis complex syndrome

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Role of a novel FGF receptor (FGFRL1) in the control of cell proliferation and tumor formation

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Systemic Gene Therapy of Hepatocellular Carcinoma by tumortargeted, self-limited E2F-1 Overexpression from the human Telomerase Reverse Transcriptase (hTERT) Promoter

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Design of new tools to improve the efficacy genotoxins

Completed research projects already presented in 2004 edition

These projects can be found at www.swisscancer.ch/research
(Text in German and French only)

Antonarakis Stylianos E. | OCS 01184-09-2001 | CHF 180,800.–
Centre médical universitaire, Division Génétique médicale, Genève
Functional analysis of LKB1, a kinase mutated in Peutz-Jeghers syndrome

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Azzi Angelo | KLS 01223-02-2002 | CHF 48,000.–
Universität Bern, Institut für Biochemie und Molekularbiologie, Bern
Inhibition of human prostate cancer cell proliferation by tocopherol: In vitro and ex vivo molecular studies

Hajnal Alex | OCS 01108-02-2001 | CHF 294,052.–
Universität Zürich, Zoologisches Institut, Zürich
Notch signaling during Caenorhabditis elegans development

Huber Marcel | OCS 01150-09-2001 | CHF 200,000.–
CHUV, Hôpital de Beaumont, Service de dermatologie, Lausanne
Development of an in vivo model for human non melanoma skin cancer

Kralli Anastasia | OCS 01224-02-2002 | CHF 147,000.–
The Scripps Research Institute, San Diego, USA
The role of the transcriptional coactivator PERC in estrogen action and breast cancer

Kühn Lukas | KLS 01000-02-2000 | CHF 308,300.–
ISREC, Epalinges
Regulation of mRNA stability in cell proliferation

Radek Skoda C. | OCS 01163-09-2001 | CHF 196,600.–
Kantonsspital Basel, Departement Forschung, Basel
The pathogenesis of myeloproliferative disorders

Rufer Nathalie | OCS 01228-02-2002 | CHF 139,500.–
NCCR Molecular Oncology, ISREC, Epalinges
Senescence and immortalization of human antigen-specific CD8+ T lymphocytes

Trumpp Andreas | KLS 01234-02-2002 | CHF 236,400.–
ISREC, Epalinges
Genetic analysis of c-myc and Pten in self-renewal and differentiation of murine stem cells



Weisse Blüten 1, 2006, 75 x 100 cm

What are “targeted cancer therapies”?

Traditionally, cancer research has rested on three pillars: surgery, radiation therapy, and medical therapy. In special cases, tumour treatment can be enhanced by immunological measures.

Medical cancer treatments to date have relied on cytotoxic drugs (“chemotherapy”) and hormones or related substances. In many cases, the effect of these substances is not specific to cancer cells; they have the same (undesirable) effects on “normal” cells in the body. This leads to well-known and in part dreaded side effects, such as nausea, hair loss, loss of resistance to infection, and more. For this reason, researchers have long been at work to develop targeted therapies that target cancer cells only and largely spare normal cells in the body.

To develop targeted therapies in oncology, the following conditions would have to be met:

- The cancer cells have to present a target that is not present in normal cells. This could be a protein, for example, that is anchored on the surface of cancer cells but not normal cells and that is crucial to the survival of the cancer cells.
- Drugs should recognise and bind to these specific molecular targets and take no notice, so to speak, of the normal cells in the body.
- Ideally, such drugs should not merely inhibit cancer cells but actually eliminate them, so that an actual cure becomes possible.

This ideal scenario has by no means been achieved. However, over the past decades, basic research and clinical research have produced many findings and insights that can be of vital importance to the success of this concept.

Basic research has taught us what molecular processes occur in cancer cells but not normal cells. In cancer cells in chronic myeloid leukaemia, for example, chromosomes 9 and 22 are combined abnormally, which results in a new fusion gene that does not exist in normal cells of the body. This fusion gene can produce an abnormal protein, the BCR-ABL protein, which “drives” the stem cells that produce blood cells to cancer. Once fitted with this molecular engine, these stem cells can proliferate abnormally and take over normal bone marrow (where blood cells originate) and eventually the entire organism – which is exactly what leukaemia is. Basic research and the pharmaceutical industry have developed molecules that block this protein in a targeted fashion; these inhibitors affect almost exclusively the abnormal and overrepresented protein in the leukaemia cells and find no partners in normal cells (including bone marrow). The result: a highly targeted therapy for leukaemia, which, according to current knowledge, does not have many side effects. The treatment of patients with chronic myeloid leukaemia with imatinib mesylate (Glivec® [Gleevec] manufactured by Novartis) was groundbreaking, and it is a fine example of a successful targeted cancer treatment.

The limits of targeted cancer therapy

Our wish list includes targeted therapies not only for rare diseases but also for the prevalent solid tumours. These include breast cancer, cancer of the large intestine, lung cancer, and others. In about one-quarter of cases, the cancer cells harbour a protein, known as HER-2/neu, which is produced in excess. Clinical studies suggest that breast cancer cells that have this protein are more aggressive than others. Over decades, antibodies were developed that can react with this protein in a targeted manner. The antibody trastuzumab (Herceptin®, manufactured by Roche) has been found to be not only effective in treating patients with breast cancer but is also tolerated well. The example of treatment with trastuzumab, however, shows that targeted cancer therapies are still beset with limitations. Although the antibody attacks the protein in a targeted fashion, not all cancer cases respond that theoretically should. In cases of metastasising breast cancer, the treatment is effective in less than half of women who present with a HER-2/neu-positive tumour. The literature reports that adjuvant (that is, preventive) administration of trastuzumab to prevent recurrences is successful in some cases, but recurrences of radically excised tumours cannot be excluded in spite of trastuzumab.

The third example of a treatment that was intended to be a targeted cancer therapy came to a black end. In various types of cancer – in lung cancer, for example – an excess is found of a protein known as “epidermal growth factor receptor” (EGFR). This protein is akin to a “satellite receiver dish” for external hormonal signals, which it sends into the cell nucleus, triggering growth. The finding of an overproduction of EGFR in lung cancer cells suggested that drugs that can suppress EGFR and the metabolic pathway that depends on it could be of use in the treatment of lung cancer. Several so-called EGFR blockers were

tested, among these gefinitib (Iressa[®], manufactured by Astra Zeneca). After initial trials had proved successful, however, several large-scale comparative studies resulted in disappointment: patients taking gefinitib did not survive any longer than patients taking placebo, and even in combination with traditional chemotherapy, Iressa[®] did not show any demonstrable advantages. The drug, which had been launched with much enthusiasm, has not really become a mainstay in the treatment of patients with lung cancer.

Crucial breakthrough not in sight

The three examples show the full range of targeted therapies, from a very successful drug to a new substance that was developed at high expense and later had to be classed as ineffective. It would therefore be unrealistic to expect a breakthrough with a few drugs in the near future. What will happen is that the targeted therapies will increasingly have their place in treating cancer – not as substitutes for surgery, radiation treatment, and chemotherapy but as additional treatments that work in many cases.

Cancer research is expensive. The amounts spent on experimental (basic) research every year are substantial, and perhaps even higher are the costs of clinical trials of new cancer drugs that the pharmaceutical companies have to pay for. This means that new cancer drugs are not likely to be cheap. However, the development and trends in pricing for new drugs that the pharmaceutical industry is demanding should be critically assessed. Many of the new drugs cost several thousand Swiss francs per month of therapy, and a correspondingly high clinical profit cannot be expected in every case. The fact that drugs are becoming ever more expensive and that at the

same time increasing numbers of cancer patients can be treated has to be borne in mind during the cost discussion in the health care system. For it would be regrettable if clinical trials reported medical advances but only the wealthier strata in the population were able to benefit.



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Clinical cancer research in Switzerland – models of collaboration

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Cancer prevalence is increasing worldwide, and cancer – depending on age group – is the second or even first leading cause of death. Research that aims to develop effective treatment methods for cancers is more necessary than ever. With regard to patients and their often severe illnesses, a high priority must be given to clinical cancer research. Clinical research is not limited to medical therapy, however; it also investigates possible ways to prevent cancer and studies care of cancer patients.

More than 40 years ago, representatives of haematology and oncology departments of several university hospitals in Switzerland that treat cancer patients formed a working group in order to cluster their efforts in the fight against cancer. This working group became the Swiss Group for Clinical Cancer Research (SAKK), with the declared aim of devoting efforts to clinical – that is, patient-oriented – cancer research. Thanks to its decentralised structure, the working group was joined over time by oncology wards of university and non-university hospitals across Switzerland. Contacts were made with cancer research groups abroad, and treatment studies were conducted in collaboration. The SAKK played a leading role in the establishment of treatment standards in clinical oncology in Switzerland. Over time, disciplines such as radio-oncology, surgery, gynaecology, and psycho-oncology were integrated in SAKK. The Swiss Paediatric Oncology Group (SPOG) was founded in the 1970s. Also at that time, the cancer registries that ex-

isted in some cantons were merged. Today, the cancer registries of the Association of Swiss Cancer Registries (VSKR) cover nine cantons. Prompting by the authorities ultimately resulted in a merger of the adult oncology group (SAKK), the paediatric oncology group (SPOG), and the cancer registries. As umbrella organisation, the Swiss Institute for Applied Cancer Research (SIAC) was founded in 1991. Along with the Swiss Institute for Experimental Cancer Research (ISREC), which focuses mainly on basic research, the SIAC was intended to be a discussion partner for politicians and authorities. SIAC's declared aim was to coordinate research activities in Switzerland and to make available new insights from cancer research as quickly as possible. Thanks to funding from the federal government, cantons, private foundations, and industry, clinical cancer research could move ahead.

Clinical cancer research today

Today, an increasing number of adults and most children with cancer are being treated in accordance with the latest findings of national and international therapy optimisation studies. There is ongoing evaluation of study results, and the findings inform new treatment approaches. In addition, prevention programmes, genetic counselling in the context of cancer, quality-of-life studies during and after cancer treatment, and economic evaluations of expensive cancer treatments have become established. Clinical cancer research has not only become more diverse; researchers are now also networked with other research groups in the clinical and basic sciences both

within Switzerland and abroad. All of these activities and the strengthened coordination between the different medical disciplines made it possible to improve, in part notably, survival rates and quality of life both in children and adults with cancer.

Clinical research is positioned in a field of both expectations and deficits. On the one hand, scientists, doctors, patients, and the public expect research projects to meet high demands as to originality and quality, and, what is more, they most of all expect rapid application of research results in everyday clinical practice. On the other hand, clinical research again and again has to contend with problems, as regards content, organisation, and structures.

To strengthen patient-oriented clinical research in Switzerland, the Swiss National Science Foundation has propagated a model for reorganisation of clinical research called "Swiss Trial Organisation". Interdisciplinary units at mainly university hospitals would provide support for all disciplines involved in clinical research. The concept foresees a two-level organisation, with local clinical trial units (CTUs) as centres of competence for clinical studies, networked via a national coordination centre ("leading house") at the national level. Standing opposite this is the already established clinical cancer research that is based on a structure oriented to the clinical presentation of cancer. This structure was developed over many years and incorporates all disciplines that deal with cancer. It includes nine regions in Switzerland, each with one

central hospital and its professional environment. This structure makes it possible to conduct clinical cancer treatment studies in all parts of the country via a central coordinating centre. A radical reorganisation decreed by law could jeopardise clinical cancer research substantially. Culture and tradition, paired with motivation and commitment to optimal patient care, are the drivers behind successful clinical cancer research in large and small hospitals and continuing into oncology specialists' practices.

Future structure

Changes in the social and health policy environment and in the structure of the population are forcing also organisations active in clinical cancer research to adapt accordingly. What is needed is an efficient, lean structure that will result in the greatest possible gains in new knowledge. The SIAK and its member associations have introduced initial restructuring already, and further steps will be taken.

The findings of patient-oriented research are the more relevant the larger the groups of patients that are included in the studies. Future structures in clinical research will therefore have to make it possible to include in clinical studies not only university treatment centres but also patients from non-university based, clinical institutions and doctors' practices. For quality improvement of patient-oriented clinical studies, centres of competence are needed, for one. For another, however, motivation to participate in clinical studies has to be developed at a broad level. The existing structures and experiences that are already established in clinical cancer research and have proved their worth, and the lessons learnt from these, should be utilised for a further development of the planned Swiss Trial Organisation for the general promotion of clinical patient-oriented research.

Here, the promotion of young talent by means of critical selection and qualified education and training is of the utmost importance for internationally competitive clinical research.

A number of different factors are impacting the development of clinical cancer research today, and they will remain in effect in future. Standing opposite the objective to one day be able to cure all people with cancer are not only financial constraints but also a growing deluge of regulatory and legal demands. Physicians engaged in clinical cancer research can not simply treat their patients according to the latest state of knowledge. For one, the financial means are limited, and for another, the legal requirements that have to be met by treatment studies conceived according to the latest insights are so extensive that the resources required in time and money are not only ever increasing but are in part prohibitive. The realisation of absolutely necessary clinical research is thus greatly jeopardised. Because of the massive effort and resources required, therapy studies for rare cancers are already today no longer being conducted. It is the patients who suffer. Our society will in future be judged also according to whether we succeed in striking a balance between successful clinical research and the ensuring of legal standards.



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Felix Niggli has been the head of the Department of Pediatric Oncology at the University Children's Hospital Zurich since 1999.

Niggli was appointed vice president of the Board of Directors of the Swiss Institute for Applied Cancer Research (SIAC) in 2004 and has acted as chairman since 2005. In addition to his work on the Scientific Committee of the Swiss Cancer League, Niggli has served in several national foundations and on international pediatric-oncological committees.

List of approved research projects

Approved projects in clinical research in 2004 and 2005 | Total funds allocated CHF 6,707,100.–

Aebersold Daniel M. | OCS 01681-02-2005 | CHF 172,800.–

Universität Bern, Inselspital, Bern

The role of activating point mutations in the Met-Receptor-Tyrosine kinase in tumor radioresistance

Ammann Roland A. | OCS 01466-02-2004 | CHF 96,600.–

Universitäts-Kinderklinik, Inselspital, Bern

A prospective multi-center study on pediatric patients with fever in severe chemotherapy-induced neutropenia. Including a randomized comparison of outpatient management and oral antimicrobial therapy versus inpatient management and intravenous antimicrobial therapy in a subgroup with low risk of adverse events (low-risk subgroup study), Swiss Pediatric Oncology Group

Arcaro Alexandre | OCS 01501-02-2004 | CHF 167,800.–

University of Zurich, Division of Clinical Chemistry and Biochemistry, Zurich

Signalling by specific phosphoinositide 3-kinase isoforms in human glioblastoma and neuroblastoma cell proliferation, chemoresistance and metastasis

Benhattar Jean | OCS 01638-02-2005 | CHF 203,000.–

CHUV, Institut de pathologie, Lausanne

Identification of biomarkers for early cancer detection in Barrett's esophagus patients using methylation profiles and the Wnt pathway

Bertoni Francesco | OCS 01517-02-2004 | CHF 166,900.–

Oncology Institute of Southern Switzerland, Bellinzona

Cancer genes involved in genetic progression of germinal centre B cell lymphomas

Dubey Raghvendra | OCS 01551-08-2004 | CHF 258,300.–

Universitätsspital Zürich, Zürich

Pathophysiological role of estrogen metabolism in breast cancer

French Lars | OCS 01748-08-2005 | CHF 194,800.–

Hôpital universitaire de Genève, Genève

Analysis of the potential of novel multimeric soluble recombination forms of the TNF-family members FasL, TRAIL, OX40L and 4-1BBL to induce tumor cell death and immunomodulation in the cutaneous T cell lymphoma Sézary syndrome

Gratwohl Alois | KLS 01520-02-2004 | CHF 193,100.–

Kantonsspital Basel, Bereich Innere Medizin I, Basel

Predicting transplant rates in haematopoietic stem cell transplantation

Hamel Christian | OCS 01579-08-2004 | CHF 303,300.–

Kantonsspital Basel, Basel

Clinical function after total mesorectal excision and rectal replacement: A prospective randomized trial comparing side to end anastomosis, Colon-J-Pouch and straight coloanal anastomosis.

A project of the SAKK (Swiss Group for Clinical Cancer Research)

Hegi Monika | OCS 01680-02-2005 | CHF 211,600.–

CHUV, Laboratoire de biologie et génétique des tumeurs, Lausanne

Implications of the p16/Arf gene and the EGFR signalling pathway in development and treatment of gliomas

Heim Markus Hermann | OCS 01475-02-2004 | CHF 168,800.–

Kantonsspital Basel, Basel

Prevention of hepatitis-C-virus-associated hepatocellular carcinoma by interferon treatment of chronic hepatitis C: the role of virus-induced interferon resistance

Hirschel Bernard | KLS 01683-02-2005 | CHF 51,100.–

Hôpital universitaire de Genève (HUG), Division des maladies infectieuses, Genève

Predictive factors for evolution of Kaposi's sarcoma in patients treated with HAART

Hitz Felicitas | OCS 01387-08-2003 | CHF 62,100.–

Kantonsspital St. Gallen, St. Gallen

Gemcitabine for the treatment of patients with newly diagnosed, relapsed or therapy-resistant mantle cell lymphoma – a multicenter phase II trial of the SAKK (Swiss Group for Clinical Cancer Research)

- Hoessli Daniel C.** | OCS01408-08-2003 | CHF 212,000.–
Centre médical universitaire, Département de pathologie, Genève
Signaling adaptors in lymphoma cell rafts: potential targets for therapeutic intervention
- Iggo Richard** | OCS 01482-02-2004 | CHF 116,700.–
ISREC, Epalinges
Microarray analysis of breast cancer in the context of a prospective neoadjuvant clinical trial
- Imhof Beat A.** | OCS 01653-02-2005 | CHF 177,600.–
Centre médical universitaire, département de pathologie, Genève
The mechanism of anti-JAM-C antibodies blocking tumor angiogenesis
- Jaggi Rolf** | OCS 01704-04-2005 | CHF 242,000.–
Universität Bern, Bern
Molecular profiling of human breast cancer from RNA derived of formalin-fixed, paraffin-embedded (FFPE) material
- Kalia Yogeshvar** | OCS 01753-08-2005 | CHF 168,600.–
Université de Genève, Genève
Non-invasive transdermal iontophoretic delivery of antiemetic drugs for the treatment of chemotherapy-induced nausea and vomiting
- Leibundgut Kurt** | OCS 01470-02-2004 | CHF 54,700.–
Universitäts-Kinderklinik, Inselspital, Bern
Platelet transfusion of single donor apheresis products in pediatric oncology: Is there a role for ABO matching?
- Maecke Helmut R.** | OCS 01778-08-2005 | CHF 100,400.–
Universitätsspital Basel, Basel
Molecular and pharmacological basis for glucagon-like peptide 1 (GLP-1) receptor targeted diagnosis and therapy of cancer: In vitro assessment of receptor expression in human neoplastic tissues – design, synthesis, preclinical and preliminary clinical evaluation.
- Mamot Christoph** | OCS 01577-08-2004 | CHF 193,000.–
Universitätsspital Basel, Basel
Use of anti-EGFR immunoliposomes to overcome drug resistance mechanisms in human cancer
- Matthes Thomas** | OCS 01781-08-2005 | CHF 201,900.–
HUG Genève, Genève
Analysis of transcription factors PU.1 and GATA-1 functions in myelodys-plastic syndromes, in acute myeloid leukemia and in leukemia stem cells
- Müller Beatrice U.** | OCS 01731-08-2005 | CHF 249,000.–
Inselspital, Bern
The master transcription factor PU.1 is essential for normal hemato-poiesis: Analysis of PU.1 alterations in patients with acute myeloid eukaemia (AML)
- Neuenschwander Hans** | OCS 01533-03-2004 | CHF 40,000.–
IOSI, Ospedale Italiano, Viganello
A randomised, control-led, double-blind study on the effects of morphine (0.5% gel) applied topically in patients with painful skin ulcers
- Pruschy Martin** | OCS 01514-02-2004 | CHF 191,200.–
Universitätsspital Zürich, Klinik für Radio-Onkologie, Zürich
Ionizing radiation and inhibition of angiogenesis: influence of the tumor milieu for this combined treatment modality
- Renevey Philippe** | OCS 01777-08-2005 | CHF 188,600.–
Centre suisse d'électronique et de microtechnique (CSEM), Neuchâtel
Development of a voice restoration system for laryngectomees in order to improve their social interaction
- Romero Pedro** | OCS 01596-08-2004 | CHF 192,700.–
Ludwig Institute for Cancer Research, Hôpital orthopédique, Lausanne
Toll-like receptor 3 ligands as multifunctional adjuvants for cancer immunotherapy
- Schäfer Werner Beat** | KLS 01473-02-2004 | CHF 193,500.–
Universitäts-Kinderklinik, Zürich
Beyond gene expression profiling: Characterization of novel diagnostic markers and therapeutic targets in pediatric sarcomas
- Singer Gad** | OCS 01506-02-2004 | CHF 168,800.–
Universität Basel, Institut für Pathologie, Basel
Identification of drug resistance genes in ovarian carcinoma



Weisse Blüten 2, 2006, 75 x 100 cm

Skoda Radek C. | OCS 01411-08-2003 | CHF 203,700.–
Kantonsspital Basel, Basel

The pathogenesis of myeloproliferative disorders

Spichiger Elisabeth | OCS 01725-08-2005 | CHF 153,000.–
Universität Basel, Institut für Pflegewissenschaft, Basel

Prevalence and evolution of symptom experience in cancer patients with focus on fatigue and anemia as its potential correlate

Stahel Rolf Arno | OCS 01491-02-2004 | CHF 80,400.–
Universitätsspital Zürich, Klinik und Poliklinik für Onkologie, Zürich

Expression profiling in malignant pleural mesothelioma patients undergoing neoadjuvant chemotherapy

Strasser Florian | OCS 01696-04-2005 | CHF 177,400.–
Kantonsspital St. Gallen, St. Gallen

E-MOSAIC: A multicentre randomised controlled trial of longitudinal electronic monitoring of symptoms and syndromes associated with advanced cancer in patients treated with chemotherapy in palliative intention

Taverna Christian | OCS 01468-02-2004 | CHF 190,400.–
Universitätsspital Zürich, Klinik und Poliklinik für Onkologie, Zürich

Comparing two schedules of rituximab maintenance in rituximab-responding patients with untreated, chemotherapy-resistant or relapsed follicular lymphoma: A randomized phase III trial of the SAKK

Thalmann George N. | OCS 01752-08-2005 | CHF 190,300.–
Inselspital, Bern

Impact of therapeutic and preventive strategies in prostate cancer on prostate-specific antigen (PSA), gene expression and tumor cell survival

von der Weid Nicolas-Xavier | KLS 01605-10-2004 | CHF 265,900.–
CHUV, Département de pédiatrie, Lausanne

Long-term outcome of childhood cancer: incidence and spectrum of late effects

Wodnar-Filipowicz Aleksandra | OCS 01664-02-2005 | CHF 301,500.–
Universitätsspital Basel, Departement für Forschung, Basel

Role of the natural killer cell receptors NCR and KIR in immune defence against human leukemia

Zucca Emanuele | OCS 01709-04-2005 | CHF 111,600.–
Ospedale Regionale Bellinzona e Valli, Bellinzona

A prospective clinico-pathologic study of Primary Mediastinal B-cell Lymphoma (PMBCL)

Zuppinger Christian | OCS 01582-08-2004 | CHF 92,000.–
Inselspital, Bern

Targeted cancer therapy and the heart: Mechanisms of carditoxicity caused by the modulation of the erbB2/HER2 signalling axis in the adult myocardium and in isolated cardiomyocytes

Scholarships in 2004 and 2005

Bucher Christoph, Lauwil | BIL KLS 01617-12-2004 | CHF 68,300.–
Role of ICOS/ICOS-L in immune responses
Destination: University of Minnesota Hospital, Minneapolis, USA

Gautschi Oliver, Bern Liebefeld | BIL OCS 01599-08-2004 | CHF 35,300.–
Die Rolle der beim Lungenkrebs überexprimierten, mitotischen Kinasen
Destination: Davis Cancer Center, University of California, Sacramento, USA

Novak Urban, Bern | BIL KLS 01522-02-2004 | CHF 68,000.–
Rolle der Activation-Induced Deaminase (AID) und der aberranten Hypermutation bei Non-Hodgkin-Lymphomen
Destination: Institute for Cancer Genetics, Columbia University, New York, USA

Schüpbach Jonas, Bern | BIL KLS 01526-02-2004 | CHF 38,000.–
Microvascular dynamics of free flaps in Head and Neck Surgery
Destination: Centre Antoine-Lacassagne, Centre Hospitalier Universitaire de Nice, Nice, France

Stern Martin, Basel | BIL OCS 01597-08-2004 | CHF 76,000.–
Ausnützung der Allo-Reaktivität von Natural-Killer-Lymphocyten bei der haploidentischen Stammzelltransplantation
Destination: Perugia University School of Medicine, Perugia, Italia

Clinical research

List of completed research projects in 2004 and 2005

Benhattar Jean | KLS 01327-02-2003 | CHF 110,700.–
CHUV, Institut de pathologie, Lausanne
Molecular basis for neoplastic progression in Barrett's esophagus

Borner Markus M. | OCS 01333-02-2003 | CHF 170,600.–
Inselspital, Institut für Medizinische Onkologie, Bern
Functional identification of regulators of cancer drug response and apoptosis in ex vivo tissue cultures of human colorectal cancer

Donaldson Sally | OCS 01181-09-2001 | CHF 223,000.–
Universitätsspital Zürich, Klinik und Poliklinik für Onkologie, Forschungslabor Molekulare Onkologie, Zürich
Biological and clinical implications of caspase-8 silencing in small cell lung carcinoma

Dummer Reinhard | OCS 01217-02-2002 | CHF 106,900.–
 Universitätsspital Zürich, Dermatologische Klinik, Zürich
Disfunctional interferon signaling in lymphoma: molecular analysis and evaluation of viral oncolysis as treatment approach

Eberle Alex N. | OCS 01213-02-2002 | CHF 95,700.–
 Kantonsspital Basel, Departement Forschung (ZLF), Universitätskliniken, Basel
Receptor-mediated targeting of human melanoma for treatment of metastases

Hegi Monika | OCS 01124-02-2001 | CHF 152,700.–
 CHUV, Laboratoire de biologie et génétique des tumeurs, Service de neurochirurgie, Lausanne
The Influence of the p16/p19 gene on brain tumor development modeling cancer pathways

Hitz Felicitas | OCS 01387-08-2003 | CHF 62,100.–
 Kantonsspital St. Gallen, Onkologie/Hämatologie C, St. Gallen
Gemcitabine for the treatment of patients with newly diagnosed, relapsed or therapy-resistant mantle cell lymphoma – a multicenter phase II trial of the SAKK (Swiss Group for Clinical Cancer Research)

Juillerat-Jeanneret Lucienne | OCS 01308-02-2003 | CHF 132,300.–
 Institut universitaire de pathologie, Lausanne
Photodynamic detection and therapy of cancer: targeting photosensitizers via the glycoside pathways

Leibundgut Kurt | OCS 01470-02-2004 | CHF 54,700.–
 Universitäts-Kinderklinik, Pädiatrische Hämatologie/Onkologie, Inselspital, Bern
Platelet transfusion of single donor apheresis products in pediatric oncology: Is there a role for ABO matching?

Mainil-Varlet Pierre | OCS 01190-09-2001 | CHF 209,200.–
 Universität Bern, Institut für Pathologie, Bern
Novel surface markers in tumors of cartilaginous origin: an evaluation of their diagnostic value

Merlo Adrian | OCS 01338-02-2003 | CHF 161,800.–
 Universitätsspital, Neurochirurgische Klinik, Basel
A combinatorial strategy with "biologicals" against human gliomas: Preclinical study how to exploit novel drugs that target growth factor and angiogenic (EGFR, PDGFR, KDR), integrin (FAK) and nutritional (mTOR) pathways

Niggli Felix | OCS 01230-02-2002 | CHF 167,000.–
 Universitäts-Kinderklinik, Zürich
Establishing of minimal residual disease techniques in childhood acute lymphoblastic leukemia and their application in the international clinical treatment trial (ALL-BFM 2000)

Pless Miklos | KLS 01231-02-2002 | CHF 238,500.–
 Kantonsspital Winterthur, Medizinische Onkologie und Tumorzentrum, Winterthur
Hybrid cell cancer vaccine for renal cell cancer, melanoma and other tumors. A clinical phase I/II study

Porzig Hartmut | OCS 01404-08-2003 | CHF 92,278.–
 Universität Bern, Pharmakologisches Institut, Bern
The role of cytokine- and G protein-dependent signaling for the development of drug resistance in human leukemia cells expressing the Bcr/Abl oncogene

Spertini Olivier | OCS 01121-02-2001 | CHF 125,700.–
 CHUV, Division d'hématologie, Lausanne
Biology of leukemia cells: role of adhesion receptors

Strasser Florian | OCS 01385-08-2003 | CHF 59,700.–
 Kantonsspital St. Gallen, St. Gallen
Randomised phase I/II – study with Ghrelin versus placebo for patients with cancer-related anorexia/cachexia

Terracciano Luigi | OCS 01172-09-2001 | CHF 88,500.–
 Schweizerische Arbeitsgemeinschaft für klinische Krebsforschung (SAKK), Bern
Investigation of tumor genotype in colorectal cancer by tissue microarray technique

Widmann Christian | OCS 01330-02-2003 | CHF 201,000.–
 Universität Lausanne, IBCM, Lausanne
Design of new tools to improve the efficacy of genotoxins

Zenhäusern Reinhard | OCS 01274-08-2002 | CHF 51,000.–
 Schweizerische Arbeitsgemeinschaft für klinische Krebsforschung (SAKK), Bern
2-CDA and rituximab as remission induction and rituximab as in vivo purging prior to peripheral stem cell mobilization in patients with chronic lymphocytic leukemia (CLL) – A prospective multicenter phase II trial

Presentation of completed research projects

Benhattar Jean | **Molecular basis for neoplastic progression in Barrett's esophagus** (KLS-01327-02-2003)

Barrett's esophagus (BE) is an acquired condition in which the normal squamous epithelium in the distal esophagus is replaced by a metaplastic columnar epithelium, as a complication of chronic gastroesophageal reflux. The clinical significance of this disease is its associated predisposition to esophageal adenocarcinoma (EAC). A large variety of genetic and epigenetic alterations seem to play a key role in the development and the neoplastic progression of Barrett's esophagus. EAC is a highly lethal disease. Therefore, the early detection of preneoplastic lesions represents one of the most promising approaches to reduce the growing number of cancers on Barrett's esophagus.

Aim of the study

Better understanding of the pathogenesis of columnar metaplasia and its progression to cancer might allow the identification of biomarkers that can be used for early diagnosis, which will improve the patient survival.

Results

During this study, an improved protocol for methylation-sensitive single-strand conformation analysis (MS-SSCA), which is used to analyze promoter methylation, was proposed. Furthermore, a methylation-sensitive dot blot assay (MS-DBA) was developed, which allows rapid, easy, and sensitive detection of promoter methylation. To establish an epigenetic profile in EAC, both methods were applied to study the methylation pattern of several promoter genes. Five promoters (APC, TIMP3, TERT, CDKN2A, and SFRP1) were found to be hypermethylated in the tumors. The promoter of APC, TIMP3, and TERT was frequently methylated in BE samples from EAC patients, but rarely in BE samples that did not progress to EAC. These three biomarkers might therefore be considered as potential predictive markers for increased EAC risk. Analysis of Wnt pathway alterations indicated that WNT2 ligand is overexpressed as early as the low-grade dysplastic stage, and downregulation by promoter methylation of the SFRP1 gene occurs already in the metaplastic lesions. Moreover, loss of APC expression is not the only factor involved in the activation of the Wnt pathway.

Conclusion and benefit to patients

These results indicate that a variety of biologic, mostly epigenetic events occurs very early in the carcinogenesis of BE. This new information might lead to improved early diagnosis and thus open the way to a possible application of these biomarkers in the prediction of increased EAC risk progression.

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Borner Markus | **Functional identification of regulators of cancer drug response and apoptosis in ex vivo tissue cultures of human colorectal cancer** (OCS 01333-02-2003)

Chemotherapy sensitivity and sensitivity to molecular targeted therapeutics are regulated by a large variety of different genes. To make things more complicated, these genes vary from tumor to tumor and from patient to patient. This project aims at analyzing the genetic pattern of chemotherapy responsiveness in colorectal tumor tissue. For this purpose, tumor tissue from patients will be treated ex vivo with conventional chemotherapy. The molecular response will be assessed by reverse-phase protein microarrays.

This new method allows us to analyze a large number of proteins of interest simultaneously. To examine the expression pattern of the proteins of interest over time, the tumor tissue will be treated ex vivo with a method that has been developed in our laboratory. We will identify characteristic protein expression patterns that are related to chemotherapy response. This method will be validated as a next step in the clinic for predictive purposes, in view of the rapidly expanding drug treatment options in cancer.

Project coordinator
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Donaldson Sally | **Biological and clinical implications of caspase-8 silencing in small cell lung carcinoma** (OCS 01181-09-2001)

Short summary of project

Tumors derived from the neuroectoderm have numerous clinical, biological, and genetic similarities. It is probable that these tumors use similar resistance mechanisms to evade anti-cancer treatments. Small cell lung carcinoma (SCLC) is one such neuroectoderm-derived tumor. SCLC is an aggressive disease, with a survival rate of only 25%.

Aim of study

In our study, we have investigated the mechanisms of resistance to apoptosis-induction used in SCLC. Methods and techniques used: Methylation-specific PCR analysis, cell death assays, Western blotting, FACs analysis, RT-PCR.

Results

Small cell lung cancer cell lines (SCLC) were tested for their sensitivity to death receptor-induced apoptosis and were found to be highly resistant to cell death induced by the death ligands FasL and TRAIL. Similar results were observed previously with invasive neuroblastoma cell lines.

Resistance of SCLC cells was associated with reduced expression of death receptors Fas and TRAIL-R1 and silencing of caspase-8 expression, a key enzyme in the death receptor pathway. In addition, analysis of SCLC tumor material demonstrated reduced levels of mRNA for Fas, TRAIL-R1, and caspase-8 in comparison to tumors from non small cell lung carcinoma (NSCLC). Treatment of SCLC cells with the demethylating drug 5'aza-2-deoxycytidine restored expression of Fas, TRAIL-R1, and caspase-8. This suggested that expression of TRAIL-R1, Fas, and caspase-8 was silenced in SCLC by methylation of their promoter regions. Methylation-specific PCR performed on 25 SCLC tumor samples revealed hypermethylation of CpG islands in the promoter regions of TRAIL-R1 (40%), Fas (40%), and caspase-8 (52%). Treatment of SCLC cells with a combination of 5'aza-2-deoxycytidine and IFN-g induced Fas, TRAIL-R1, and caspase-8 expression and increased sensitivity to death-receptor-induced death.

In summary, SCLC cells are highly resistant to the induction of apoptosis via the death receptor pathway. This resistance is due to the silencing of critical components of the signaling pathway via DNA methylation.

Project coordinator
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Dummer Reinhard | **Dysfunctional interferon signaling in lymphoma: molecular analysis and evaluation of viral oncolysis as treatment approach**
(OCS 01217-02-2002)

Cutaneous T cell lymphomas (CTCL) regularly present defects in the interferon (IFN)-signaling system, making them refractory to interferon-dependent immunomodulatory and antiproliferative effects. As a consequence, CTCL cells become highly susceptible to infection with oncolytic viruses.

In the first part, our results show clearly that defects in the IFN-signaling pathway occur, however, at different steps of the IFN-signaling cascade. We observed in several SS-derived cell lines a strongly reduced activation of STAT1, the major transcription factor of both the IFN- α/β and the IFN- γ -signaling pathway.

To improve screening for IFN defects, we evaluated whether the IFN-signaling defects could be rapidly determined by using reporter genes under the transcriptional control of IFN- α/β - or IFN- γ -responsive promoter/enhancer elements. To this purpose, we transfected reporter plasmids into SS cells that were subsequently stimulated with IFN- α or IFN- γ . Indeed, no induction of the reporter gene in the presence of IFN- α or IFN- γ was detectable. However, assessment of the expression of the endogenous MxA gene in response to IFN- α or the GBP in response to IFN- γ was clearly more sensitive. Therefore, we developed instead a semi quantitative RT-PCR assay for MxA that allows rapid assessment of defects in the IFN- α -signaling

pathway, since MxA is exclusively induced by IFN- α . Similarly, we are currently setting up a RT-PCR assay for the IFN- γ -induced GBP.

Second, we developed an oncolytic Semliki forest virus (SFV) vector and evaluated its potential as an oncolytic virus. The prototype strain of SFV is highly sensitive to the action of IFN- α/β and shows pronounced cytolytic activity in SS cells. In order to identify the viral component responsible for the IFN-sensitive phenotype of the prototype strain of SFV, we cloned the entire genomic RNA of the prototype SFV strain and of the highly IFN-resistant L10 strain. We were able to show that none of the viral proteins was responsible for the IFN-sensitive phenotype, but we identified at the 5' and 3' untranslated regions of the SFV virus what is called an "interferon sensitivity determining element" (ISDE). Our virus is virulent in IFN-resistant cells but highly attenuated in IFN-sensitive cells exposed to IFN- α , and it is hence a primary candidate for an effective oncolytic virus of IFN-resistant tumors.

Taking advantage of the highly IFN- α/β sensitive live attenuated measles virus (MV) vaccine, we carried out a phase I dose escalation trial with five CTCL patients. The receptor for the MV vaccine strain (CD46) is expressed on the surface of CTCL cell lines and tumor biopsies of the five patients. Viral infection of tumor cells induced syncytia formation and subsequently cell death. For safety reasons, the measles vaccine virus was administered only after systemic pretreatment with a high dose of IFN- α , and only patients with preexisting antimeasles antibodies were selected. The virus was applied intralesionally. We verified by immuno-histochemical and histological analyses of biopsies local infection by the virus, syncytia formation, and subsequently cell death. CTCL are thus a promising target for a virus-based oncolytic therapy.

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Eberle Alex | **Receptor-mediated targeting of human melanoma for treatment of metastases**
(OCS 01213-02-2002)

Melanoma has an increasing incidence rate that is greater than for any other form of cancer in Europe, the United States, and Australia. The probability of developing metastases originating from a primary melanoma lesion with >4 mm thickness is about 50%, whereby regional lymph nodes are the first to be affected. Sentinel lymph node biopsies, together with imaging methods (PET, CT, ultrasound), make it possible to diagnose melanoma metastases with good accuracy, but the detection of micrometastases (frequent for melanomas) as well as the treatment of these remain an unsolved problem.

The research project addressing the topic of *receptor-mediated targeting of human melanoma for the treatment of metastases* is based on the concept of bringing therapeutic molecules or principles specifically into cancer cells by use of a carrier molecule. For melanomas, the peptide

hormone α -MSH (α -melanocyte-stimulating hormone) has been chosen, because it exerts a functional role in melanocytes and melanoma cells (induction of pigment formation); melanoma cells frequently overexpress the MSH-specific membrane receptor MC1-R (melanocortin-1 receptor), which represents that target for cellular internalization of α -MSH and related molecules. Thus, the therapeutics coupled to MSH-like molecules can be taken up by melanomas with good specificity relative to other tissues, except for the kidneys, where they also accumulate unspecifically. One of the aims of the study is to find molecules that yield a high tumor-to-kidney ratio.

As therapeutic principles, we apply metal radioisotopes, which are inserted into the MSH molecules using the DOTA chelator that is chemically linked to the peptide. After internalization into tumor cells, short-range ionizing β - or α -radiation impairs tumor cell growth and/or destroys tumor cells. For preclinical *in vitro* and *in vivo* experiments, longer-range diagnostic positron- or γ -radioisotopes or toxins are used with which receptor activity and abundance, relative accumulation in the tumor, half life, and effectiveness are being tested. So far, only a very small number of experiments have been carried out in the clinic, and they need to be repeated before conclusions can be drawn.

Until now, several new MSH molecules have been prepared and successfully tested *in vitro* and *in vivo* in animal models, which yielded an excellent accumulation in metastatic melanoma lesions: radioactivity is found almost exclusively in tumor cells, and only little is delivered to the surrounding healthy tissue. At present, we are carrying out comparative studies with new MSH carrier molecules containing different charges or other additions (e.g., sugar moieties) in order to further increase the tumor-to-kidney ratio. However, many more experiments in the laboratory and with experimental animals will be required before melanoma patients will eventually benefit from this therapy concept.

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Hegi Monika | **The influence of the p16/19Arf gene on brain tumor development. A mouse model for human glioblastoma** (OCS 01124-02-2001)

Glioblastoma is the most common and most malignant neoplasm of the human nervous system. The prognosis of patients with glioblastoma remains poor, with a median survival of only 15 months even with the newest standard of care, including surgery, chemo- and radiotherapy. Thus, new avenues have to be taken to improve treatment strategies for this devastating disease, including targeted treatments. In glioblastoma the EGF receptor is known to be frequently amplified and overexpressed, or constitutively activated in the mutant form EGFRvIII. The biological consequences are activation of gene transcription leading to enhanced proliferation, progression through

cell cycle and inhibition of apoptosis, major requirements for tumor growth and resistance to treatment. Hence, the EGFR is a particularly attractive target for treatment. The activation of the EGFR pathway is commonly associated with deletions of the *CDKN2A^{p16/Arf}* gene locus that encodes two tumor suppressor genes p16 and Arf (p19 in the mouse), suggesting a cooperative effect. The aim of this project was to understand the implications of the two alterations in the development of glioblastoma by modeling this pathway in mice and in an *in vitro* system using mouse astrocytes.

The cooperative effect was studied by transplanting neuroectodermal cells (embryonic brain cells) deficient for p16/19 and overexpressing EGFR or EGFRvIII into the brain of mice. Gliomas developed at a low penetrance, exclusively from cells deficient for both copies of the *p16/p19* gene and expressing EGFRvIII, hence supporting the notion of a cooperative effect. In order to understand underlying molecular mechanisms for this cooperation, we used a specific small molecule EGFR inhibitor. Despite the fact that we could demonstrate inhibition of EGFR or EGFRvIII, downstream signaling via ERK could only be prevented in presence of a functional *p16/19* gene locus. Thus, the tumor suppressor genes p16 and/or p19 may play a crucial role in a feedback loop. Therefore, they may need to be inactivated in the development of glioblastoma to render cells permissive for an activated EGFR pathway, by this means exerting a cooperative effect that is selected for in human glioblastoma.

These results obtained through *in vivo* and *in vitro* approaches are of high relevance and will contribute to the understanding of the signaling pathways involved in resistance to specific EGFR inhibitors. Recent clinical trials have shown that despite overexpression of the target, EGFR or EGFRvIII, only few patients benefited from specific EGFR inhibitors, indicating the need for more in depth analysis of underlying molecular mechanisms implicated in resistance to treatment.

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Hitz Felicitas | **A multicenter phase II trial testing Gemcitabine for the treatment of patients with newly diagnosed, relapsed, or chemotherapy-resistant mantle cell lymphoma (MCL)** (OCS 01387-08-2003)

MCL is currently an incurable disease, with a median survival of 3 years. Despite an intensive therapeutic approach in first-line regimens, most patients suffer an early relapse of their disease. The median age of 63 years at diagnosis and comorbidities in this age group do not allow aggressive treatment regimens. These two arguments obliged us to test Gemcitabine in newly diagnosed, not otherwise treatable, or in relapsed or refractory patients.



Weisse Blüten 3, 2006, 75 x 100 cm

The master protocol are phase 2 studies for MCL testing Gemcitabine with the primary end point of objective response and the secondary end points: adverse reactions, time to progression, response duration, time to treatment failure, and molecular response.

Between August 2004 and March 2006 a total of 18 patients were included in the protocol. According to the statistical design a tested substance is of interest if there is a response of 30%. If the response rate with a substance is $\leq 10\%$, corresponding to response in one or no patient after the evaluation of 10 patients, the study protocol will be closed.

The stage 1 analysis showed a PR (partial response) in 1 patient; 5 patients reached a SD (stable disease); and 4 had to stop early due to PD (progressive disease). Therefore, accrual was stopped in March 2006. Hematotoxicity rate is low and very few nonhaematological toxicities, such as oedema and fatigue, were documented.

PCR amplification of *VDJ-rearranged* immunoglobulin heavy chain (*IgH*) genes revealed a clonal band used for direct sequencing in 9 cases. V_H mutational status was defined in these cases, and V_H somatic hypermutations (homology $\leq 99\%$) were identified in 4 cases. The distribution of silent and replacement mutations in the complementarity-determining region II (CDR II) and in framework III (FR III) revealed an *at random* and an *antigen-selected* pattern in two cases each.

PCR amplification of the t (11; 14) (q13; q32) (BCL1/JH rearrangement) chromosomal translocation was used to detect and monitor minimal residual disease. Material from 14 cases was analyzed at baseline: 14 blood and 10 bone marrow samples. 6 cases had a positive PCR for the t (11; 14) (q13; q32); all of them were positive in both blood and bone marrow. Follow-up material in at least one time point was available in 4 cases. A persistence of the molecular marker was observed in all the cases.

We can conclude that Gemcitabine is well tolerated in the administered schedule but has low efficacy as monotherapy in MCL. Stabilization of the disease in a mostly elderly and heavily pretreated patient group is an acceptable result. Results of the total number of 18 treated patients and the evaluation of the secondary end points are pending.

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Juillerat-Jeanerret Lucienne | **Photodynamic detection and therapy of cancer: targeting photosensitizers via the glycoside pathway** (OCS-01308-02-2003)

The lack of cell selectivity of anticancer agents results in side effects. The rational targeting of therapeutics, that is, the development of cell-selective anticancer agents, represents important improvement of therapies. Photodynamic therapy (PDT) is a cancer treatment modality involving tumor destruction by light after loading tumor cells with a photosensitizer.

Objectives of the project

Glycosylation is important in many cell functions, thus carbohydrate-dependent cellular pathways may be potential new targets for innovative therapies of human cancer, such as photodynamic therapy. Our proposal was to evaluate cell-specific targeting using glycolytic pathways of aminolevulinic acid (ALA)-glycosides as precursors of the photosensitizer protoporphyrin IX.

Methods

- 1) The determination of *glycosidases activities* in living human cells and in cell extracts was performed using commercial substrates and human tumor cells of various origins, endothelial cells and fibroblasts in culture, to quantify the relative activities of several glycosidases.
- 2) Pyrrolidine-based α -mannosidase inhibitors were designed, synthesized, and evaluated for their biological effects in cells to determine whether *glycosidase inhibitors* may have the potential to control tumor cell growth.
- 3) *ALA derivatives of mannose, glucose, and galactose* were designed, synthesized, and evaluated in human cells to determine whether they are efficient precursors of the photosensitizer protoporphyrin IX.

Results

- 1) The determination of cellular glycolytic activities demonstrated that β -galactosidases, α -glucosidases, and α -mannosidases were intracellular and were higher in human tumor cells than in human fibroblasts, whereas β -mannosidases, β -glucosidases, and α -galactosidases were not potential targets in tumor cells.
- 2) The design, synthesis and biological evaluation of α -mannosidase inhibitors demonstrated that the concept of targeting this glycosidase was valid as a new modality of cancer therapy, since these inhibitors decreased tumor cell survival more efficiently than that of fibroblasts, suggesting some cell selectivity.

- 3) The design, synthesis, and biological evaluation of glucoside-ALA derivatives demonstrated that these molecules were effective precursors of the photosensitizer protoporphyrin IX in human cancer cells.

Benefit to patients

These results suggest that defined glycosidases have the potential to be used for devising new therapeutic approaches for cancer therapy and for tumor cell targeting of photosensitizers or other therapeutic drugs, opening new therapeutic opportunities for cancer patients.

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Leibundgut Kurt | **Platelet transfusion of single donor apheresis products in pediatric oncology: Is there a role for ABO blood group matching between donor and recipient?** (OCS 01470-02-2004)

Background

The main purpose of platelet transfusions in pediatric oncology is prevention or treatment of bleeding in patients with malignancies who have low platelet counts caused by their disease or its treatment.

For transfusion of red blood cells, ABO blood group matching between donor and recipient is strictly required. However, for platelet transfusion, it is common practice to discount ABO matching, in particular because storage time of platelet concentrates is restricted to a maximum of 5 days and platelets have to be transfused within this time.

Aim of the study

The aim of this prospective study was to investigate the response to platelet transfusions in pediatric patients. These patients were infants, children, and young adults with cancer undergoing chemotherapy causing reduced platelet production due to suppressed bone marrow function. The main question was: Is there a difference in the platelet increment comparing ABO-blood-group-matched with unmatched transfusions. The unmatched group can be divided in two subgroups: major or minor mismatched transfusions.

Methods

Platelet counts before and 1 hour after transfusion were determined, and the increment, after correction for the recipient's body surface, was expressed as a standardized value (CCI). To document compatibility of platelet transfusions, different clinical parameters before, during, and after transfusion were recorded.

Results

Analysis of 400 platelet transfusions (70.5% matched) showed a 25% higher increment when matched platelets were transfused as compared with mismatched transfusions. Increments after major mismatched transfusions were even 36% lower in comparison to matched transfusions. Analysis of subgroups revealed a highly significant negative effect on transfusion efficacy when platelets from donors with blood group A1 were transfused to re-

ipients with blood group O or B. CCI was 48% lower as compared to matched transfusions. Increments after platelet transfusion with platelets from donors with blood group A2 to recipients with blood group O or B were comparable to increments after matched transfusions.

Benefit to patients

To minimize the number of transfusions, an optimal increment should be the aim of platelet transfusions for all patients needing platelet support. Our data indicate that at least in the investigated pediatric population, platelet transfusions from donors with blood group A1 to recipients with blood group O or B should be avoided, because the increments were only half that of matched transfusions. In case identical platelets are not available, platelets from donors with blood group A2, but not A1, can be given to recipients with blood group O or B, resulting in good increments.

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Mainil-Varlet Pierre | **Novel surface markers of cartilaginous origin: an evaluation of their diagnostic value** (OCS 01190-09-2001)

Outline of the study

The prevalence of primary malignant bone tumors is estimated at 1:100,000 within the general population, 17–24% of which are malignant cartilaginous tumors (chondrosarcomas). The histologic distinction between the different entities is made based on cell type/differentiation, matrix formation, and architecture, combined with radiodiagnostic and clinical data. Despite the relative indolence of most benign forms and the slow evolution of well-differentiated malignant tumors, anaplastic forms (dedifferentiated chondrosarcomas) count among the most fulminant and deadly human tumors. Given the metastatic potential of chondrogenic tumors and their poor responsiveness to conventional chemotherapy or radiotherapy, surgery is the mainstay of treatment. In collaboration with the Department of Pathology of the University of Leiden and the Institute of Pathology of the Mayo Clinic, Minnesota (USA), the proposed study aims at the identification and characterization of chondrogenic tumor markers.

Aim of the study

The identification of specific surface markers as prognostic tools that can be used in immunohistochemistry would strongly improve the diagnostic tools available to the pathologist. To identify potential prognostic factors we investigated the expression patterns of certain differentiation antigens in normal chondrocytes as well as in chondrogenic tumors.

Methods

- 1) Selection of chondrogenic tumors (enchondromas, chondrosarcomas of different grades).
- 2) Classification and histopathological diagnosis of the biopsies; grading of the chondrogenic tumors.

- 3) Phenotypic analysis of the neoplastic cells using fluorescence-activated cell sorting (FACS).
- 4) Histopathological and immunohistochemical analysis of the paraffin-embedded biopsies.

Results

Human native articular cartilage and human primary chondrosarcoma tumors were collected according to ethical guidelines and digested with a cocktail of pronase and collagenase. Isolated chondrocytes were then analyzed using a panel of selected CD antibodies using fluorescence-activated cell sorting (FACS). We characterized the distribution profile of several CD markers on chondrocytes and the modulation of their expression patterns in tumorous conditions. We found complete loss of CD44 (hyaluron receptor) expression on grade III chondrosarcomas, whereas CD44 is moderately expressed in grade I and grade II chondrosarcomas and very strongly expressed on metastatic cells. The adhesion molecule CD44 is implicated to play a pivotal role in signal transduction pathways between chondrocytes and extracellular matrix. CD44 is therefore a potential candidate tumor marker for chondrogenic neoplasias; however, further investigations are needed to fully evaluate the diagnostic value of CD44 expression patterns. Ongoing work will focus on refining the immunohistochemical analysis and performing RT-PCR analysis to assess any phenotypical drift in metastatic components from primary malignant tumors.

Benefit to patients

The identification and characterization of novel surface markers in tumors of cartilaginous origin will help to improve the diagnosis of chondrosarcomas.

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Merlo Adrian | **A combinatorial strategy with “biologicals” against human gliomas: Preclinical study how to exploit novel drugs that target growth factor and angiogenetic (EGFR, PDGFR, KDR), integrin (FAK) and nutritional (mTOR) pathways** (OCS 01338-02-2003)

Introductory remark

High-grade glioma remains one of the most difficult cancers to treat. In these tumors, oncogenic EGFR pathway triggers downstream PI3K/RAS-mediated signaling cascades. It has been found in transgenic mice models that mimic gliomagenesis that glioblastoma (GBM) cannot develop upon single, but only on simultaneous activation of the EGFR-signaling mediators RAS and AKT. However, *in vitro* as well as clinical studies have shown that complete blockade of EGFR activation is not sufficient to induce apoptosis in human GBM cells. This suggests additional cross talk between downstream pathways. A further new strategy to attack cancer is inhibiting histone deacetylases (HDIs). HDIs act on chromatin density of a limited number of epigenetically regulated genes promoting differentiation, cell cycle arrest, and apoptosis in tumor cells.

Goal of the study

One goal of this preclinical study was to assess whether combinations of compounds that inhibit nonoverlapping pathways may be attractive strategies to treat gliomas. A major focus addressed the role of the PI3K/AKT and the RAS/RAF/MEK/ERK-signaling cascades in the cell-intrinsic survival program of GBM cells. In addition, combinations of metabolic blockade of the insulin-signaling pathway and HDI were tested.

Methods

We investigated combination therapies using protein kinase inhibitors (PKI) against EGFR (AEE788), PDGFR (Gleevec), and mTOR (Rapamycin analogue RAD001), assessing GBM cell survival. In addition, AEE788 was tested in combination with the microtubule inhibitor patupilone. The HDI LAQ 824 was assessed to treat GBM cells, alone and combined with 2-deoxy-D-glucose (2-DG), a glycolysis blocker within the insulin-signaling pathway. The drugs used were kindly provided by Novartis Oncology, Basel.

Results

Clinically relevant doses of AEE788, Gleevec, and RAD001 alone or combined did not induce GBM cell apoptosis. In contrast, simultaneous inactivation of the EGFR downstream targets MEK and PI3K by U0126 and Wortmannin triggered rapid tumor cell death. Blocking EGFR with AEE788 in combination with sublethal concentrations of the microtubule stabilizer patupilone also induced apoptosis and reduced proliferation of GBM cells, accompanied by reduced AKT and ERK activity. When studying metabolic interventions in combination with HDI, we found that the glycolytic inhibitor 2-DG, combined with low doses of the HDI LAQ824, induced strong apoptosis in all tested glioma cell lines, in a p53-independent manner. Further, we found that 2-DG neutralized the LAQ824-dependent p21 upregulation. In the same way, HDI, like trichostatin (TSA) or sodium butyrate (NaB), when combined with 2-DG, induced strong apoptosis and decreased p21 levels. Similarly, the 2-DG/LAQ824 combination synergized in tumor cell lines of other origins such as breast and cervix.

Benefit to patients

These results allow the conclusion that drug combinations that downregulate both ERK and PKB/AKT activities may prove effective in overcoming GBM cell resistance. Clinical trials will have to show whether such concepts based on *in vitro* models can be translated into the clinical arena. In addition, histone acetylation and the energetic pathways are targets to be considered for novel combined therapies against gliomas and other tumor types. Again, clinical trials will eventually prove this promising new concept to be of practical relevance for GBM patients.

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Niggli Felix | **Establishing of minimal residual disease techniques in childhood acute lymphoblastic leukemia and their application in the international clinical treatment trial (ALL-BFM 2000)** (OCS 01230-02-2002)

Study design

Approximately 75–80% of children with acute lymphoblastic leukemia (ALL) can be cured with current treatment protocols. However, as there is still a significant number of patients who will eventually relapse, this indicates that in many cases not all leukemic cells will have been eradicated. Furthermore, there is a substantial number of children with ALL that could have been cured with less toxic treatment, allowing them to experience a better quality of life. In the past several risk factors have been described in ALL. Recent investigations have found that the dynamics of the decrease of tumour burden after initiation of treatment can have a major influence on the outcome of the disease. Monitoring of minimal residual disease (MRD) in patients with leukemia is therefore a very important diagnostic tool to assess treatment response and an individual's risk of relapse.

Aim

The goal of this proposal was to establish a Swiss reference laboratory for PCR-based minimal residual disease quantitation in childhood ALL and to monitor minimal residual disease (MRD) in patients treated in the current international treatment protocol.

Methods

Within childhood ALL, rearrangements of immunoglobulin and T-cell receptor genes serve as specific markers for an individual leukemic clone. The use of real-time quantitative PCR technology permits accurate quantification of these markers and allows detection of one leukemic cell in 1,000 to 1,000,000 normal cells, thereby increasing the sensitivity by a factor 10–10,000 over conventional cytomorphology. Monitoring of minimal residual leukemic cells in leukemia with high accuracy and sensitivity was performed during treatment at different given time points.

Results

A total of 92 patients with ALL were analyzed in the period 2003–2005. The majority of patients (80%) had two Ig and/or TCR-sensitive markers, with a further 15% having just a single marker. For most markers the sensitivity was 10⁻⁴ or higher. For all precursor B-ALL and T-ALL patients in the cohort, a total of 149 specific gene rearrangements were detected. The majority of the children included in this study were treated according to the international ALL 2000 study of the BFM (Berlin-Frankfurt-Münster) group. Preliminary results indicate that the dynamics of clearance of MRD is one of the strongest predictive factors for survival. MRD monitoring is now also part of the ALL-relapse trial and will be integrated in a future ALL-BFM treatment trial. Furthermore, identical methods are under investigation for stratification of adult ALL patients.

Significance

The techniques of MRD analysis in leukemia at different time points allow risk-adapted treatment of childhood leukemia. Treatment intensity may be reduced in cases with a rapid clearance of minimal residual leukemic cells

in the bone marrow, whereas in patients with a delayed disappearance of leukemic cells, treatment has to be intensified or modified in order to obtain better survival rates.

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Pless Miklos | **Hybrid cell cancer vaccine for renal cell cancer, melanoma, and other tumors. A clinical phase I/II study** (KLS 01231-02-2002)

To obtain a functional tumor vaccine, two conditions have to be met: First, there have to be tumor-associated antigens, which are not present on normal tissues, and which have to be recognized and attacked by the immune system; however, such tumor-associated antigens are often not known. Second, in order to induce an effective immune response, these tumor antigens have to be processed by antigen-presenting cells, such as dendritic cells (DC), and then be presented to the cytotoxic T lymphocytes. There is an elegant and simple way to fulfill these two conditions: DCs can be electrically fused with tumor cells. These hybrid cells contain all relevant tumor antigens and, at the same time, can present those antigens effectively to T cells due to the presence of DC characteristics. Because whole autologous (i.e., from the patient) tumor cells are used, *all* tumor antigens are represented in the vaccine, whether they are known or not.

Patients with progressive renal cell cancer or melanoma can be included in the study. First, small parts of the tumor are removed during an operation. They are processed to single cells and then fused electrically with DCs. The DCs are obtained and generated from healthy blood donors. The hybrid cells are then irradiated with 200 Gy. All patients receive the vaccine once every 4 weeks subcutaneously. Every 2 months a follow-up exam with CT is performed.

So far, 24 of 29 patients with renal cell cancer have been vaccinated, 3 women and 21 men. There were a total of 129 vaccines given (a median of 4). There were no severe side effects, only a few cases of mild fever or rash at the injection site. Specifically the following results were obtained: 6 patients showed tumor progression, in 10 patients the tumor growth could be stopped temporarily (for a duration of 4–17 months). In 3 patients tumor shrinkage could be observed. The last patient had a mixed response: some of the tumor manifestations were shrinking, while others were growing. It is too early to assess the results in the last 4 included patients. The results of the patients with melanoma are still immature; so far only 8 patients have been included.

These results show that for patients with renal cell cancer, it is feasible to generate an effective and well-tolerated vaccine, using the hybrid cell method. However, so far our goal to achieve a 20% response rate was missed. Therefore, the optimized conditions for improved efficacy still have to be worked out.

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Porzig Hartmut | **The role of cytokine- and G-protein-dependent signaling for the development of drug resistance in human leukemia cells expressing the Bcr/Abl oncogene** (OCS 01404-08-2003)

Overview

Some forms of leukemia, in particular chronic myeloid leukemia (CML), are induced by a chromosomal rearrangement within early hematopoietic progenitor cells, leading to a deregulated form of the endogenous Abl tyrosine kinase (Bcr/Abl). Recently, a specific inhibitor of this enzyme (Imatinib, Gleevec®) has been introduced that successfully blocks the proliferation of leukemic cells in a high proportion of patients. Resistance to this drug may develop in later stages of the disease, e.g., due to Abl mutations. However, it has remained unclear how affected cells can survive the long lag time required for a resistant cell population to develop in spite of continuous drug treatment.

Aim of the study

Earlier results from our laboratory had shown that erythropoietin, an endogenous cytokine growth factor for erythroid progenitor cells, could promote the survival of Bcr/Abl carrying erythroid cells in the presence, but not in the absence, of imatinib. In the current study we explored the underlying mechanisms and tested whether these earlier observations could be generalized to Bcr/Abl expressing myeloid and lymphoid cell lines.

Methods

We used several human leukemic cell lines with and without constitutive Bcr/Abl expression and a mouse pre-B cell line conditionally expressing Bcr/Abl under the control of an inducible promoter. In these cells we monitored the activities of Abl and Src-type tyrosine kinases, of protein kinase C (PKC) isoforms and G-protein-coupled receptor-induced Ca²⁺ transients as a function of imatinib treatment. These cellular signaling systems are all known to be intimately linked to the regulation of survival and proliferation of hematopoietic cells.

Results

Bcr/Abl tyrosine kinase activity proved to be strongly linked to an amplification of cellular Ca²⁺ transients. Receptor-mediated Ca²⁺ influx as well as Ca²⁺ release from intracellular stores are inhibited by protein kinase C (PKC). Bcr/Abl enhances Ca²⁺ influx by reducing specifically the activity of subtype α of PKC. This is an important

observation, because, unlike normal cells, Bcr/Abl expressing leukemic cells depend for survival to a large extent on transmembrane Ca^{2+} influx. Selective inhibition of Bcr/Abl enzymatic activity by imatinib not only reversed its stimulating effect on Ca^{2+} fluxes but also abolished autonomic growth in favor of cytokine-dependent growth and survival. Myeloid and lymphoid hematopoietic progenitor cell lines all developed resistance to imatinib if endogenous myeloid growth factors like granulocyte colony-stimulating factor (G-CSF) or interleukin-3 are made available.

Therapeutical applications

Our results explain how endogenous hematopoietic growth factors facilitate the survival of mutated leukemic cells in the presence of imatinib. To avoid the development of drug resistance, it is therefore essential to eliminate Bcr/Abl-positive cells by combining drugs with different mechanisms of action already at the start of the therapeutic regime.

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Spertini Olivier | **Biology of leukemia cells: role of adhesion receptors** (OCS 01121-02-2001)

Leukemic cell dissemination is a major complication of acute myeloblastic (AML) and lymphoblastic leukemia (ALL). Blast cell migration is dependent on mechanisms that are similar to those that regulate leukocyte migration into inflammatory lesions. Among the involved adhesion receptors, PSGL-1 (P-Selectin Glycoprotein Ligand-1) is constitutively expressed by blast cells and supports leukemic cell rolling on platelet or endothelial selectins. PSGL-1 interaction with selectins is dependent on post-translational modifications such as sialylation, sulfation, N- and O-glycosylation. Among the involved enzymes, the α 1,3-fucosyltransferases (FucT) play a major role in generating cell surface glycoconjugates carrying fucosylated oligosaccharides, which interact with selectins (sLe^x, Le^x, VIM-2, CLA).

We examined here the expression of α 1,3-fucosyltransferases by leukemic blast cells obtained from 120 patients with acute leukemia. FucT-IV and FucT-VII mRNAs were detected, by RT-PCR, in all tested cases. In contrast, the presence of FucT-IX mRNA was shown in only 40% of patients with acute leukemia (48/120). FucT-IX mRNA was detected in 65% of AML (47/72) and, less frequently, in 26% of ALL (11/42). Importantly, all ALL cases expressing FucT-IX were either secondary leukemia resulting from the transformation of chronic myelocytic leukemia in acute lymphoblastic leukemia or mature B-ALL (FAB L3 subtype or Burkitt lymphoma/leukemia according to WHO classification). FucT-IX was not detected in precursor B or T-ALL.

The role of FucT-IV, FucT-VII, and FucT-IX in the biosynthesis of Le^x, VIM-2, CLA, and sLe^x was examined by expressing the cDNA of each α 1,3-FucT in CHO cells. Immunophenotypic analysis of CHO transfectants indicated

that FucT-VII synthesizes sLe^x and CLA but not Le^x or VIM-2. Lex and CLA were generated by both FucT-IV and FucT-IX. FucT-IV and FucT-IX differed in their ability to synthesize VIM-2, FucT-IX being less efficient than FucT-IV. The role of FucT-IX in regulating selectin-dependent rolling was assessed under hydrodynamic flow conditions. P-selectin-dependent interactions were transient and occurred at high velocities (median: 497.95 mm/s, n=96). In contrast, much slower rolling velocities were observed on E-selectin (median: 7 mm/s, n=64). The recruitment of CHO-C2F9PSGL-1 and CHO-C2F7PSGL-1 cells was similar on E-selectin (mean \pm SEM: 127.44 \pm 4.38, n=5 vs 151.16 \pm 3.16 cells/min/mm², n=5). On the other hand, CHO-C2F4PSGL-1 cells were less efficiently recruited on E-selectin (54.20 \pm 2.13 cells/min/mm², n=5).

These results indicate that FucT-IX is involved in the biosynthesis of Lex, VIM-2, and CLA and that it confers E-selectin-binding activity to CHO cells. In contrast to FucT-IV and FucT-VII, FucT-IX had a minor role in regulating P- and L-selectin-dependent rolling on CHO transfectants. The frequent expression of FucT-IX in myeloblasts suggests that it may participate with FucT-IV and FucT-VII in regulating E-selectin-dependent cell migration into tissues.

The identification of molecules involved in regulating blast cell adhesion is critical to the understanding of mechanisms supporting blast dissemination. In addition, it will allow the design of molecules aimed at inhibiting blast cell adhesion and dissemination in a microenvironment supporting their survival.

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Strasser Florian | **Randomised phase I/II – study with ghrelin versus placebo for patients with cancer-related anorexia/cachexia** (OCS 01385-08-2003)

This randomized, placebo-controlled, double-blind, double cross-over phase I/II study compared an intravenous pre-lunch infusion of Ghrelin or placebo (days 1/8 or 4/11) in advanced cancer patients. In preclinical studies Ghrelin influenced key mechanisms of the frequent and devastating anorexia/cachexia syndrome (ACS): hypothalamic appetite and energy regulation, upper gastrointestinal motility, proinflammatory cytokines, and anabolic hormones.

The aim of this trial was to assess safety and tolerability (primary objective) and preliminary efficacy. Patients with ACS and any tumor were eligible that could feed themselves, had no major secondary ACS (prebaseline palliative oncology visits), and had either no chemotherapy or a stable chemotherapy of two months' duration.

Baseline assessments were 4–5 days before day 1, end-of-study at days 17/18. On treatment days, fasting hormone levels were drawn, patients ate a standardized breakfast, completed symptom assessments, and had EKGs (auto-



Weisse Blüten 4, 2006, 75 x 100 cm

onomic function). Treatment was from 10:30–11:30 am using a second venous access. Acute symptoms (visual analogue scales: appetite, hunger, satiety, nausea, anxiety, fatigue) and hormone blood levels were monitored. In the canteen a volunteer documented each lunch (NIL) component before and after eating by weight and photographs.

Ghrelin (GMP-quality: Merck Biosciences, Switzerland) or normal saline (prepared in the pharmacy) was titrated up (20% each 2 minutes) and maintained 50 minutes. The low-dose group (LD) received 10 pmol/kg/min (equals 0.0336 mcg/kg/min, approx. 2 mcg/kg), based on maximal GH-stimulation in human volunteers and suspected ghrelin resistance in ACS. The following high-dose group (HD) received 40 pmol/kg/min.

Drug-related adverse events (CTC-Toxicity Criteria) did not differ between Ghrelin and placebo in the 21 patients on LD (7 vs. 14) and HD (19 vs. 13); two patients dropped out after day 8. No unexpected acceleration of tumor

growth was observed. Ghrelin treatment was preferred at d8 by 8/10 pts of LD and 9/11 (82%) of HD, and at d17/18 by 6/9 and 6/10 (60%), respectively.

At study start NIL was 642 kcal (SD 284) for LD and 424 (196) for HD. NIL and symptoms were not different; however, intra- and inter-individual variability were high. A positive trend of 5% NIL increase in HD and 15% of patients not receiving concurrent chemotherapy was seen. Weight and body composition remained unchanged. Analysis of autonomic function is ongoing. Total Ghrelin levels were higher ($p < 0.05$) for HD at d17/18 (3,580 pg/ml) than study start (990), but not for LD (950/1,000), active Ghrelin, GH, or IGF-1.

In conclusion, Ghrelin is well tolerated and safe in patients with advanced cancer, who preferred Ghrelin more than placebo, without significant changes in nutritional intake

or symptoms. Higher levels of Ghrelin at study end may suggest carry-over effects. In a next trial we will explore schedule (bi-daily, patients' subcutaneous application) and dose modifications (individual dose escalation).

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Terraciano Luigi | **Investigation of tumor genotype in colorectal cancer by tissue microarray technique** (OCS 01172-09-2001)

Study overview

Colon cancer is a leading cause of cancer-related death in Western societies. Its development and progression is driven by a series of molecular alterations in cancer cells, many of which are poorly understood. Of the molecular changes that are known to occur in colon cancer, little is known about their clinical significance, especially their prognostic and predictive importance. Based on a SAKK study investigating the quality and long-term outcome of surgery in colorectal cancer, tumor samples will be collected from all patients and will be stored in a tissue bank for further analysis using the tissue microarray technology (SAKK 40/00).

Aim of the study

The aim of this study is to install a tissue bank of normal and tumor tissue from colorectal cancer patients to perform molecular and cytogenetical analyses for clinically important biomarkers in colorectal cancer.

Methods and procedures

Tissue microarrays allow the simultaneous analysis of hundreds of tumors in one examination. Multiple replicate array blocks are generated, each having samples from the same tumor specimens at identical coordinates. Depending on the thickness of the original tissue, between 100 and 200 sections can be cut from each array block. This enables extensive analyses of even small primary tumors, thereby preserving precious tumor specimens for future investigations. In the tissue array technology appropriate stained sections are made from each selected primary tumor block to define representative tumor samples. Tissue cylinders are then punched from each primary tumor block and brought into a recipient paraffin block containing up to 1,000 individual samples. Multiple 4 m sections of the recipient block are then cut and can be used for immunohistochemical and FISH analysis. Those genes that appear to be the most interesting in colon cancer biology at the moment will be analyzed further.

Results

So far more than 850 normal and tumor samples have been collected and stored in a tissue bank at the Institute of Pathology of the University of Basel. In a next step the

expression patterns of different markers will be studied using tissue microarray technology and immunohistochemical as well as molecular analyses will be performed.

Benefit to patients

The clinical relevance of this research project lies in the description of biomarker patterns that may allow the development of more tailored and individualized treatment for patients with colorectal cancer. The aim would be to avoid unnecessary treatment or to design more targeted treatment modalities, thus improving the quality of life of the affected individuals.

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Widmann Christian | **Design of new tools to improve the efficacy of genotoxins** (OCS 01130-02-2003)

Treatment of many cancers relies on the combined action of several genotoxins (e.g., cisplatin). These treatments induce cell death (apoptosis) in tumor cells but also in normal sensitive cells (i.e., cells found in the blood). The detrimental effect of genotoxins on normal cells can be the cause of severe side effects. One major challenge in anticancer therapy is thus to increase the selectivity of current treatments toward cancer cells in order to spare normal cells. Our focus is to derive a genotoxin-sensitizing product from RasGAP, a protein that we have shown to contain a domain that increases the sensitivity of tumor cells, but not normal cells, towards genotoxins.

We have identified the minimal sequence within RasGAP that still bears the ability of potentiating apoptosis in response to genotoxins, and we have rendered this sequence cell-permeable. The resulting construct, called TAT-RasGAP₃₁₇₋₃₂₆, efficiently sensitized the cell death response induced by genotoxins when applied to various cancer cells. Importantly, TAT-RasGAP₃₁₇₋₃₂₆ did not sensitize nontumor cells.

In order to use the TAT-RasGAP₃₁₇₋₃₂₆ peptide in vivo, we increased its stability by converting its amino acids from the natural L-form to the protease-resistant D-form. To best mimic the structure of the natural peptide, the sequence of the D-peptide was inverted, generating what is known as the retro-inverso form. This peptide, called D-TAT-RasGAP₃₁₇₋₃₂₆, was no longer degraded in biological fluids. Moreover, D-TAT-RasGAP₃₁₇₋₃₂₆, in comparison to the L-form, better sensitizes tumors to the action of genotoxins.

To better understand the mode of action of D-TAT-RasGAP₃₁₇₋₃₂₆, we further characterized the molecular pathways it regulates. We have determined that D-TAT-RasGAP₃₁₇₋₃₂₆ sensitizes tumor cells only in the presence of a functional p53 protein. This indicates that the tumors that could potentially be treated with D-TAT-RasGAP₃₁₇₋₃₂₆ need to bear at least one copy of nonmutated p53.

To assess the efficacy of D-TAT-RasGAP₃₁₇₋₃₂₆ in vivo, nude mice injected with HCT116 human colon cancer cells were left untreated or injected with cisplatin alone or in combination with D-TAT-RasGAP₃₁₇₋₃₂₆. This peptide increased the ability of cisplatin to hamper the growth of HCT116 tumors in mice. D-TAT-RasGAP₃₁₇₋₃₂₆ therefore represents a promising tool to increase the efficiency of chemotherapies.

The benefit for patients with a cancer is that tumors sensitized by the D-TAT-RasGAP₃₁₇₋₃₂₆ compound could be treated with lower doses of genotoxins with decreased adverse side effects.

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Zenhäusern Reinhard | **2-CDA and rituximab as remission induction and rituximab as in vivo purging prior to peripheral stem cell mobilization in patients with chronic lymphocytic leukemia (CLL) – A prospective multicenter phase II trial** (OCS 01274-08-2002)

Study overview

Chronic lymphocytic leukemia (CLL) is characterized by clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen. CLL accounts for approximately 30% of all adult leukemias in Western countries.

CLL has long been treated only in palliative intentions, because long-term complete remission could not be reached with standard therapies. However, the development of novel therapeutic pharmaceuticals, such as 2-CDA, a purine analogue, and rituximab, an anti-CD20 antibody, changed this situation. 2-CDA has proven to have an impressive therapeutic activity as single agent, and the combination of rituximab with other cytostatic drugs has shown good results in the treatment of lymphoma.

In this trial 2-CDA is combined with rituximab as a non cross-reacting agent. Rituximab is added with the aim to increase the Complete Remission (CR) rate during induction chemotherapy before stem cell collection for autologous transplantation.

Aim of the study

The main aim of this phase II trial is to assess the efficacy and tolerability of the combination of 2-CDA and the monoclonal antibody rituximab as induction therapy in patients with CLL. The primary endpoint of the trial is the CR rate of the 2-CDA/rituximab combination regimen.

Methods and procedures

Patients who meet all criteria are registered for the trial. Initially, all patients obtain one cycle of 2-CDA followed by 3 cycles of 2-CDA and rituximab to induce remission. Patients who achieve a CR or Very Good Partial Remission (VGPR) or Nodular Partial Remission (NPR) and suc-

cessfully complete stem cell collection are considered for randomization between no further treatment (arm 1) and high-dose chemotherapy with autologous stem cell transplantation (arm 2).

Results

In this trial the combination of 2-CDA and rituximab has been studied for the first time. The proportion of patients reaching a CR after induction treatment with 2-CDA and rituximab is about 20%, which is about the same as could be reached by 2-CDA alone.

Benefits to patients

The results described above do not indicate any benefit for patients by combining 2-CDA with rituximab as induction therapy.

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Further research projects completed in 2004 and 2005

Dr. med. Christian Gygi | KLS 01222-02-2002 | CHF 26,900.–

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Benefits of using new tests to reduce the frequency of unnecessary prostate biopsies

PD Dr. med. Claudio Redaelli | KLS 01221-02-2002 | CHF 62,900.–

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claudio.redaelli@insel.ch

Adenovirus-mediated gene transfer of endostatin to inhibit angiogenesis in a rat model of hepatocellular carcinoma

Dr. phil. Ronald Simon | OCS 01285-08-2002 | CHF 83,500.–

Kantonsspital Basel, Institut für Pathologie, Schönbeinstrasse 40, 4031 Basel

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ronald.simon@unibas.ch

G-protein-coupled receptor 35 as a tumor marker and therapeutic target for colon cancer

Prof. Dr. Marcus Thelen | OCS 01084-09-2000 | CHF 148,600.–

Istituto di Ricerca in Biomedicina, Via Vincenzo Vela 6, 6500 Bellinzona

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marcus.thelen@irb.unisi.ch

Regulation of nuclear activities by HsPI3K-C2a and its possible involvement in cell cycle control

Completed research projects already presented in 2004 edition

These projects can be found at www.swisscancer.ch/research
(Text in German and French only)

Aebi Stefan | KLS 00986-02-2000 | CHF 224,700.–

Klinik/Poliklinik für Med. Onkologie, Universität Bern, Inselspital, Bern
Retinoids and cytotoxic drugs in ovarian cancer

Aubert John-David | KFS 01070-09-2000 | CHF 188,800.–

CHUV, Division de pneumologie, Département de médecine, Lausanne
Endothelin expression and function in lung cancer

Bischof Delaloye Angelika | KFS 00991-02-2000 | CHF 82,900.–

CHUV, Service of Nuclear Medicine, Lausanne
Preclinical evaluation of new strategies aiming to improve efficacy of radioimmunotherapy with chimeric anti-CD20 antibody in non Hodgkin B cell lymphoma

Mach Jean-Pierre | OCS 01083-09-2000 | CHF 164,300.–

Université Lausanne, Institut de biochimie, Epalinges
Tumor targeting of antigenic MHC peptide complexes conjugated to antitumor antibody fragments for induction of specific tumor cell lysis by T lymphocytes

Schäfer Beat W. | OCS 01189-09-2001 | CHF 167,000.–

Universitäts-Kinderklinik, Abteilung für Onkologie, Zürich
Gene expression profiling of pediatric sarcomas

Stahel Rolf Arno | KFS 01063-09-2000 | CHF 114,800.–

Universität Zürich, Departement für Onkologie, Zürich
Validation of survivin as a therapeutic target in pediatric and adult solid tumors – sensitization to chemotherapy and death receptor signaling



Wasser 4, 2006, 112 x 88 cm

Research in psycho-oncology

A look at the research policies of the partner organisations OncoSuisse and Swiss Cancer League and at the granted funding shows that psycho-oncological research in Switzerland is well developed, addresses up-to-date clinical and scientific issues, and will be equal to future challenges. This finding notwithstanding, psycho-oncological research still seems to exist in the shadows, although psychosocial support for cancer patients and for the practice of oncology are gaining in importance. For this reason, it is important for the partner organisations to continue their efforts to promote research in psycho-oncology.

In its beginnings, which date back to the development of psychosomatic medicine in the 1930s, psycho-oncology research focused on the psychogenesis of cancer – that is, the question as to whether certain cancers can be associated with certain psychological factors. Clinicians asked questions such as “Are there personality types that are more prone to developing tumours?”, “Can unresolved trauma, losses suffered, or sadness and grief cause cancer?”, or “Are there connections between psychological symptoms, such as depression, and cancer?” It was never possible to answer these questions scientifically. Today, it is agreed that the questions were based on a distorted approach, because they referred exclusively to those cancer patients that sought out psychotherapeutic help – that is, to a minority of patients, who had psychological problems and were therefore not representative of all cancer patients.

Later, psycho-oncology research focused increasingly on the impact of cancer and cancer treatment on patients' psychological well-being, on how cancer patients adjust to their illness, and on the role of psychosocial factors – social support in particular – that can be attributed to the ability of patients to cope with their illness. This body of research found that some 30% of patients experience mental disorders during their illness (depressed mood, anxiety, diminished ability to think or concentrate, or indecisiveness, or problems in adapting), such that they could benefit from psychiatric or psychotherapeutic intervention. Subsequently, a number of scientific studies demonstrated the importance of psycho-oncology interventions for better adaptation of patients to their illness.

Specific studies found a link between patients' psychological and immunological status. However, we still do not know today whether the effect of changes to the immune system that can be ascribed to psychological factors – such as stress, for example – are so strong that they can be graded as clinically relevant. Other studies, which investigated the effect of psycho-oncological interventions on the survival of patients, yielded contradictory results. It is safe to assume, however, that psychologically balanced patients have a higher degree of autonomy and good adaptive abilities, adhere better to treatment, make use of the medical help on offer more fully, and see their doctors in good time.

Psycho-oncological research of the future is likely to address topics such as shared decision making, communication between carers and patients, psychosocial aspects of genetic testing, and preventive interventions, or the conflicts between what is medically possible and financially possible.

In the last report on Cancer Research in Switzerland (*Krebsforschung in der Schweiz*, 2004), Alexander Kiss of Basel pointed out that unfortunately, too few high-quality research proposals had been submitted (to the Swiss Cancer League) for grants. The partner organisations started a specific support initiative that proved effective in raising the standard of psychosocial cancer research, however: Young psycho-oncology researchers were given the opportunity to obtain further education and training abroad. For instance, Daniele Stagno, of the Psychiatric Liaison Service at University Hospital Lausanne (Centre Hospitalier Universitaire Vaudois, Lausanne, CHUV), did an 18-month internship at the Memorial Sloan-Kettering Cancer Center in New York and learnt about the research methods employed there.

So that psychosocial research does not have to compete for funding with other research areas, such as basic research, the partner organisations created a separate category for grant applications from the fields of epidemiology, psycho-oncology, and care. This was also a contributing factor to today's increased opportunities for psycho-oncology researchers to obtain research grants and realise projects.

Since 2001, the partner organisations have supported some 20 research projects in psycho-oncology, with funds of about CHF 3.5 million. The projects have tackled a multitude of topics that can be regarded as up-to-date and future challenges to oncology – such as, for example, the experience of illness and adapting to it, communication between carers and those who are being cared for, psychotherapeutic interventions for cancer patients, decision-making in the choice of a cancer therapy, and psycho-oncology research in paediatric oncology.

Although there have been definite improvements in psycho-oncological research in Switzerland in recent years, the field is still restricted to a few centres and closely affiliated with just a few persons, all of them belonging to the first generation of psycho-oncology researchers. For a new generation to gain a foothold, the partner organisations will have to continue their targeted promotion of young scientists and their efforts to see that this research area does not remain limited to a handful of university centres but instead is to be found everywhere in Switzerland where cancer patients are treated.



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In 2002, there were 15,219 deaths from cancer in Switzerland, accounting for 25% of all deaths. The number of new cases – estimated from a network of cancer registries covering about 60% of the Swiss population – is approximately 32,000 (\pm 5,000). The number of prevalent cancers (that is, living persons who have had a cancer diagnosed within the last five years) in Switzerland is about 100,000.

In Switzerland, as in Western Europe and North America, cancer mortality rose throughout most of the past century until the late 1980s, but the death rate has declined appreciably over the last two decades in both men and women. This corresponds to the avoidance of about 1,500 deaths per year as compared to the peak rates of the 1980s.

These favourable trends are due to falling lung cancer mortality rates in men, from a peak of 46/100,000, world standard population, in the 1980s to 34/100,000 in 2000–2001. This is essentially due to the declined prevalence of tobacco smoking in men over the last few decades, since 80–85% of all lung cancers in men, 60–70% lung cancers in women, and almost 30% of all cancer deaths are due to smoking. Still, according to a survey on smoking in a sample of 2000 subjects representative of the Swiss adult population aged 15–74 years conducted in September 2005, cigarette smoking prevalence was 23.6% in men and 21.1% in women.

In women, lung cancer mortality has steadily increased during the last few decades, reaching an age-standardised rate of 11/100,000 in 2002. The spread of tobacco smoking in Swiss women has in fact been relatively recent, with substantial increases during the 1970s (i.e., among generations born after 1950). Consequently, in Switzerland as in the European Union, lung cancer is approaching colorectal cancer as second cause of cancer deaths. However, lung cancer mortality in women is still about 40% lower than breast cancer and remains appreciably lower than in North America. This underlines the importance of integrated and effective intervention toward smoking control in women, in order to prevent female lung cancer mortality in Switzerland from reaching the extremely high levels registered in the United States and in some countries of Northern Europe, such as Denmark and the United Kingdom.

Among other tobacco-related cancers, recent declines have been observed in men for pancreas and bladder cancers. The favourable trends in bladder cancer mortality may also be due to reduced occupational exposure to aromatic amines.

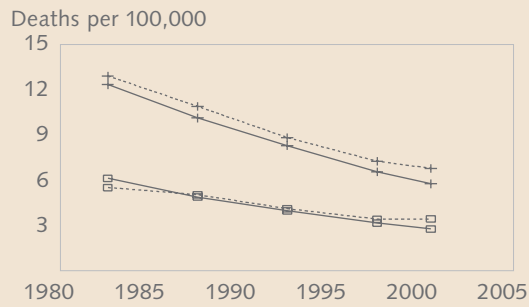
Prof. Dr. med. Fabio Levi

Fabio Levi is director of the Cancer Registries of Vaud and Neuchâtel at the Centre Hospitalier Universitaire Vaudois (CHUV, University Hospital of Canton Vaud) in Lausanne. Levi also heads the Cancer Epidemiology Unit at the Institute of Social and Preventive Medicine of the University of Lausanne (IUMSP).

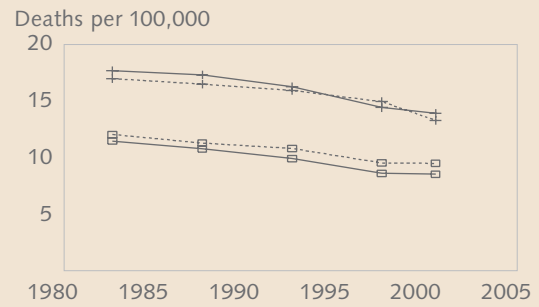
Trends in age-standardised (world population) death certification rates per 100,000 men and women for 5 selected cancers or groups of cancers plus tobacco-related, alcohol-related and total cancer mortality in Switzerland between 1980 and 2001.

(Source: WHO mortality database)

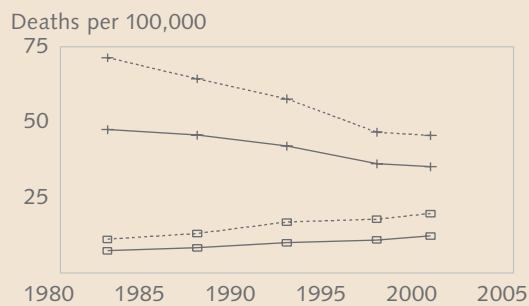
Stomach



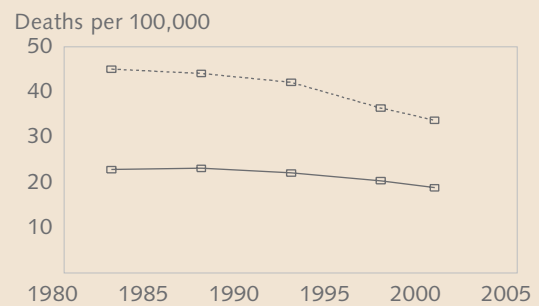
Colon, rectum and anus



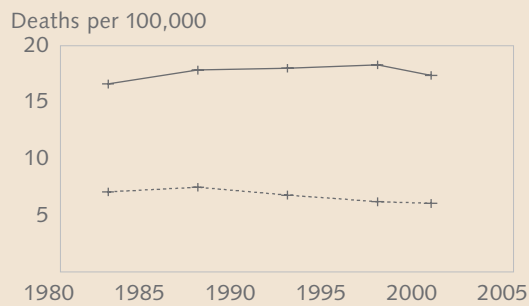
Trachea, bronchus and lung



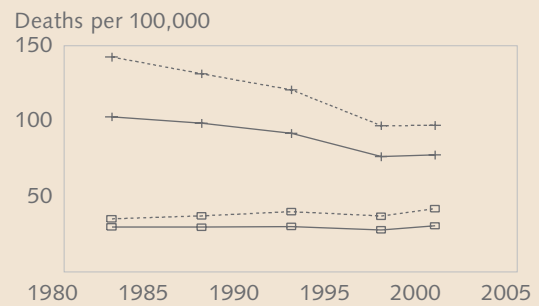
Breast



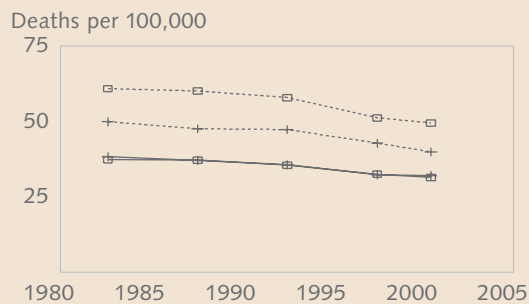
Prostate



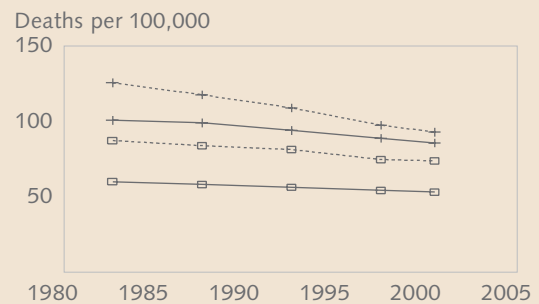
Tobacco-related neoplasms*



Alcohol-related neoplasms**



All neoplasms, benign and malignant



+ Men: +—+ all ages +.....+ age 35-64
 o Women: o—o all ages o.....o age 35-64

* include mouth or pharynx, oesophagus, stomach, liver, pancreas, lung, bladder, kidney, and leukaemias

** include mouth or pharynx, oesophagus, colorectum, liver, larynx, and breast

Likewise, cancers of the oral cavity and pharynx, oesophagus, and larynx have been appreciably declining. For these neoplasms, a major role is played by alcohol together with tobacco consumption. Recent declines in alcohol consumption therefore have played a relevant role in the decrease in head and neck cancers in Switzerland, as also observed in France and Italy.

The steady decline of gastric cancer mortality has continued, with a 30% fall over the last decade, and stomach cancer is now relatively rare in Switzerland. Likewise, cervical cancer mortality has steadily declined (–36%) over the last decade.

A more recent phenomenon is the fall of colorectal cancer mortality (–7% in men, –17% in women) over the last decade, together with the decline in female breast cancer mortality (–18%).

Besides lung cancer in women, mortality has been increasing up to most recently only from non-Hodgkin's lymphomas and multiple myelomas.

Some of the favourable trends in cancer mortality registered over recent years, including of the trends in colorectal and breast cancers, are stronger in the young and the middle-aged, and they are partly or largely due to improvements in therapy, which have also had a major impact on leukemias, Hodgkin's disease, testicular cancers, and most childhood cancers.

The falls in mortality from breast and colorectal cancers are in part attributable to screening and early diagnosis, which is a major determinant of the decline in cervical cancer mortality.

Improvements in diet, including better food preservation and a wider availability of fresh vegetables and fruits all year round have been major determinants in the decline in gastric cancers but also in most recent declines in colorectal cancers. Further, improved water sanitation, and hence control of *Helicobacter pylori*, has contributed to the favourable trend for gastric cancer.

Mortality from some of the neoplasms, which tended to rise up to the mid-1980s, has levelled off since then. These include ovary and prostate cancers, mainly in persons below the age of 70 or 75. For ovarian cancer, the declines in younger middle-aged women are due to the widespread use of oral contraceptives in generations born after 1930. For prostate cancer, the recent favourable trends are due to improvements in surgery and medical treatment (anti-androgen), while it is too early to assess any potential impact of the widespread adoption of the prostate-specific antigen (PSA) testing in the general population. Likewise, the earlier rises in skin melanoma have been levelling off, probably following campaigns for screening and early diagnosis as well as primary prevention by reducing acute exposure to sunshine and sunburns.

European Code Against Cancer (third version)

Many aspects of general health can be improved, and many cancer deaths prevented, if we adopt healthier lifestyles:

1. Do not smoke. If you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.
2. Avoid obesity.
3. Undertake some brisk, physical activity every day.
4. Increase your daily intake and variety of vegetables and fruits: eat at least five servings daily. Limit your intake of foods containing fats from animal sources.
5. If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a man or one drink per day if you are a woman.
6. Care must be taken to avoid excessive sun exposure. It is specifically important to protect children and adolescents. For individuals who have a tendency to burn in the sun active protective measures must be taken throughout life.
7. Apply strictly regulations aimed at preventing any exposure to known cancer-causing substances. Follow all health and safety instructions on substances which may cause cancer. Follow advice of National Radiation Protection Offices.

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There are public health programmes that can prevent cancers developing or increase the probability that a cancer may be cured:

8. Women from 25 years of age should participate in cervical screening. This should be within programmes with quality control procedures in compliance with European Guidelines for Quality Assurance in Cervical Screening.
9. Women from 50 years of age should participate in breast screening. This should be within programmes with quality control procedures in compliance with European Guidelines for Quality Assurance in Mammography Screening.
10. Men and women from 50 years of age should participate in colorectal screening. This should be within programmes with built-in quality assurance procedures.
11. Participate in vaccination programmes against hepatitis B virus infection.

Despite these persisting declines in mortality from several cancers, the target of a 15% reduction in total cancer mortality between 2000 and 2015 remains uncertain. This is partly due to the minor contribution of stomach cancer, which, despite continuous favourable trends, is now a rare disease. Thus, to reach the target it is necessary to improve tobacco control with a first aim to reduce the total prevalence of smoking to below 20% by 2010 and to 15% by 2015.

Targeting a 15% reduction of cancer mortality in Europe up to year 2015, that is, saving yearly 300,000 lives, the European Commission launched the new European Code against Cancer (see box) in June 2003. Although the scientific evidence is wide and complex, the Code sends very clear messages to the public:

1) Many cancers can be avoided by adopting a healthier lifestyle. In practical terms: do not smoke, avoid obesity, engage in regular physical activity, eat a varied diet (rich in fruit and vegetables and low in animal fats), moderate consumption of any type of alcoholic beverages, avoid excessive sun exposure, especially in children and adolescents, and avoid any exposure to known cancer-causing substances; and 2) tumours can be treated, or the perspective of cure can be substantially improved if timely diagnosis is made. Participate in screening programmes for breast, cervical, and colorectal cancer and pay attention to signs and symptoms like naevus changing in shape or colour, modification in bowel or urinary habits, persisting symptoms like cough, and so on. In such cases, medical examination is required and appropriate diagnostic strategy will be applied.

From perspective of the health and social costs as well, prevention remains the most useful and convenient strategy for people to reach elderly age in good health. A 15% fall in total age-standardised cancer mortality rates by 2015 is in line with the European projections and would imply a stabilisation of the total number of cancers and cancer deaths in Switzerland to around 15,000 per year, with the consequent major impacts on the health care system and budget, also in consideration of the substantial cost of newer therapies for cancer.



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Professor Fabio Levi was awarded the Swiss Cancer League Cancer Prize 2005 worth CHF 10,000.

Fabio Levi is director of the Cancer Registries of Vaud and Neuchatel at the Centre Hospitalier Universitaire Vaudois (CHUV, University Hospital of Canton Vaud) in Lausanne. Levi also heads the Cancer Epidemiology Unit at the Institute of Social and Preventive Medicine of the University of Lausanne (IUMSP). From 1991–2001 Levi was a member of the Scientific Committee of the Swiss Cancer League. Levi's research accomplished pioneering work in the implementation of the cancer registries.

In his epidemiological studies, Levi focused particularly on the health consequences of tobacco consumption and diet as well as on the development of cancer mortality in Switzerland and the European Union. His findings on the dangers of "light" low-tar cigarettes in particular had great impact. Levi's studies on the prevention of breast cancer and cancer of the large intestine contributed to the initiation of prevention programmes in these areas by the Swiss Cancer League.

Fabio Levi has been full professor at the Faculty for Biology and Medicine at the University of Lausanne since 1992. He is a member of numerous organisations and associations in the field of epidemiology and cancer and a member of the Editorial Board of the *American Journal of Cancer* (since 2001) and the journal *The Breast* (since 2005). In addition, Levi serves regularly as specialist editor for a number of professional journals in oncology and epidemiology.

Cancer Prize 2006

Prof. Alexander Kiss of the Division of Psychosomatic Medicine at University Hospital Basel, and Dr. med. Hans Neuenschwander of the Oncology Institute of Southern Switzerland (IOSI), were the winners of the Cancer Prize of the Swiss Cancer League. In honour of their achievements, Kiss and Neuenschwander will share the prize amounting to CHF 10,000. The presentation of the award took place on 16 November, 2006, at the National Cancer Conference 2006 in Bern.

The Cancer Prize of the Swiss Cancer League

To recognise people who have made outstanding contributions to the field of prevention, early detection, and the fight against cancer, the Swiss Cancer League has awarded the Cancer Prize since 1960. The prize is not awarded every year. The most recent prize winners were Prof. Dr. Nancy Hynes in 2003, for her work in molecular biology, and Dr. Jürg Bernhard in 2001, for his contributions to research on the quality of life of cancer patients.

List of approved research projects

Approved projects in psychosocial research and epidemiology in 2004 and 2005 | Total funds allocated CHF 2,280,720.–

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Aebi Stefan | OCS 01534-03-2004 | CHF 181,000.–

Universität Bern, Inselspital, Bern

Assessment of the effect of a nurse specialist service for breast and gynaecological cancer care in a Swiss hospital

Bernhard Jürg | KLS 01648-02-2005 | CHF 70,200.–

Coordinating Center Quality of Life Office, IBCSG, Bern

Communication about treatment options and clinical trials: A randomized controlled trial of a consultation skills training package

Eychmüller Steffen | OCS 01776-08-2005 | CHF 170,000.–

Kantonsspital St. Gallen, St. Gallen

Palliative Care Services in Switzerland: from a national survey to the development of a specific monitoring instrument

Gutzwiller Felix | OCS 01484-02-2004 | CHF 120,300.–

Universität Zürich, Institut für Sozial- und Präventivmedizin, Zürich

Medical end-of-life decision-making among Swiss physicians with regard to cancer patients with particular consideration of the types of organisation

Kiss Alexander | OCS 01519-02-2004 | CHF 197,100.–

Kantonsspital Basel, Basel

End of life and death in human stem cell transplantation (HSCT): a qualitative study in doctors, nurses and bereaved families

Langewitz Wolf | KLS 01666-02-2005 | CHF 130,000.–

Universitätsspital Basel Psychosomatik/Innere Medizin, Basel

Breaking bad news – do we teach professionals what patients need?

Levi Fabio | OCS 01633-02-2005 | CHF 265,620.–

Institut de médecine sociale et préventive, Lausanne

An integrated network of case-control studies on cancer: nutrition, other environmental and genetic factors

Levi Fabio | OCS 01467-02-2004 | CHF 270,000.–

Registre vaudois des tumeurs, Institut universitaire de médecine sociale et préventive, Lausanne

Monitoring and investigation of cancer mortality in Europe

Lutz Jean-Michel | KLS 01499-02-2004 | CHF 98,000.–

Registre genevois des tumeurs, Genève

Cancer survival in Europe, North America, Australia and Japan: the CONCORD study participation of the Swiss Cancer registries network in the second phase high resolution

Rössler Wulf | KLS 01649-02-2005 | CHF 43,100.–

Psychiatrische Universitätsklinik Zürich, Klinische und Soziale Psychiatrie, Zürich

Tobacco use and mental disorders correlates and causal interrelationships

Schanz Urs | OCS 01772-08-2005 | CHF 52,400.–

Universitätsspital Zürich, Zürich

Yes or no stem cell transplantation – which aspects have to be considered in the decision-making process concerning further treatment?

Stiefel Friedrich | OCS 01585-08-2004 | CHF 53,900.–

CHUV, Service de psychiatrie de liaison, Lausanne

Development of an adequate method to assess meaning in life of cancer patients with advanced disease

Stiefel Friedrich | OCS 01595-08-2004 | CHF 163,600.–

CHUV, Service de psychiatrie de liaison, Lausanne

Effects of communication skills training on oncology clinicians' communication styles and defense mechanisms

Tamm Michael | KLS 01518-02-2004 | CHF 281,000.–

Kantonsspital Basel, Basel

Optimizing care in patients with newly diagnosed bronchial carcinoma: Evaluation of their needs and of a patient-centered intervention



Wasser 5, 2006, 112 x 88 cm

Znoj Hansjörg | KLS 01645-02-2005 | CHF 79,700.–
Universität Bern, Institut für Psychologie, Bern
Mindfulness intervention for parents of pediatric cancer patients

Znoj Hansjörg | OCS 01741-08-2005 | CHF 104,800.–
Universität Bern, Institut für Psychologie, Bern
Posttraumatic personal growth and posttraumatic stress in patients and their partners adapting to cancer

Scholarships in 2004 and 2005

Lannen Patricia, Bern | BIL OCS 01598-08-2004 | CHF 19,800.–
Aufmerksamkeitslenkung und persönliche Reife als wichtige Therapieaspekte in der Psychoonkologie
Destination: Center of Mindfulness Worcester, University Amherst, Massachusetts, USA

Shaha Maya, Suhr | BIL OCS 01532-03-2004 | CHF 86,400.–
Psycho-oncological issues in cancer care
Destination: John Hopkins University, Baltimore, Maryland, USA

List of completed research projects in 2004 and 2005

Bitzer Johannes | OCS 01278-08-2002 | CHF 55,200.–

Universitätsspital-Frauenklinik, Gynäkologische Sozialmedizin und Psychosomatik, Basel

Development and evaluation of a cognitive-behavioral intervention for the treatment of body image problems and difficulties with sexuality for women after mastectomy

Bouchardy Christine | OCS 01380-08-2003 | CHF 219,400.–

Registre genevois des tumeurs, Genève

Epidemiologic research on the impact of genetic factors in breast cancer occurrence among the female population in Geneva: A study from the first familial breast cancer registry in Switzerland

Langewitz Wolf | OCS 01185-09-2001 | CHF 261,400.–

Universitätsspital Basel, Psychosomatik/Innere Medizin, 4031 Basel

Evaluation of the Swiss Cancer League communication skills Program for clinical oncologists and oncology Nurses

Stiefel Friedrich | OCS 01585-08-2004 | CHF 53,900.–

CHUV, Service de psychiatrie et de liaison, Lausanne

Development of an adequate method to assess meaning of life in cancer patients with advanced disease

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Presentation of completed research projects

Bitzer Johannes | **Development and evaluation of a cognitive-behavioral intervention for the treatment of body image problems and difficulties with sexuality for women after mastectomy** (OCS 01278-08-2002)

Treatment for breast cancer can lead to significant changes in body image and sexuality that ask for an additional adaptation process. The research project aimed at the development of a specific psychological group program for breast cancer survivors with body image problems and sexual difficulties and to gain experience with the realization of the intervention.

A first phase focused on the development of the intervention, which follows a structured approach. The program manual was elaborated on the basis of a review of the relevant literature on body image and sexual problems after breast cancer and in addition on the basis of clinical experience. The group sessions included providing participants with specific information on body image and sexuality after breast cancer and conducting concrete interventions that aim at a change in experience and coping with the respective difficulties.

In the second phase we gained initial experiences with the implementation of the program. Before and after the 10-week intervention, information on well-being, body image, sexuality, partnership, and quality of life was collected using validated questionnaires.

The results show distinct improvements in different domains of sexuality (excitement, lubrication, satisfaction, and pain). As for body image problems, we observed improvements in feeling of attractiveness, accentuation of one's own appearance, and a reduction in body-related

insecurity. In addition, improvements were reported regarding role and emotional functioning. The stability of depressive symptoms and anxiety over the course of the intervention program indicate that the above-mentioned improvements can not be regarded as indirect effects of an improvement in mood, but that they instead represent specific effects of the intervention.

In oncological after-care, only rarely are themes such as body image or sexuality addressed by the physician. On the part of the patient, however, questions related to these topics are frequent, and psychological strain may persist. Increased sensitivity on the part of physicians is the basis for detection of patients in need of further support in coping with the body image and sexual aftermath of breast cancer and for motivating them to participate in specific support programs.

Project coordinator

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Wasser 7, 2006, 112 x 88 cm

Bouchardy Christine | **Epidemiologic research on the impact of genetic factors in breast cancer occurrence among the female population in Geneva: A study from the first familial breast cancer registry in Switzerland** (OCS 01380-08-2003)

Background

Using information from the Geneva Familial Breast Cancer Registry, we evaluated the impact of a strong family risk on diagnosis and treatment in all of the 824 women diagnosed with breast cancer before the age of 50. Presence of a strong familial risk led to neither more "surveillance-detected" tumors nor earlier stage at diagnosis. However, young breast cancer patients with a strong family history were more often treated with systemic therapy. After adjustment, there was no difference in breast cancer mortality, except in the subgroups of very young patients and those treated without chemotherapy.

Aim of the study

One of the most important risk factors for breast cancer is the occurrence of breast or ovarian cancer among family members. Treatment guidelines for breast cancer patients with an increased familial risk are not well established, and conflicting data exist on the impact of a strong familial risk on the outcome of breast cancer. We

evaluated the impact of familial risk on tumor characteristics, treatment, and survival of early-onset (50 years of age) breast cancer patients.

Materials and methods

We used data from the Geneva Familial Breast Cancer Registry, which prospectively records the complete family history of cancer for every woman diagnosed with breast cancer in the canton. Using multivariate analysis we compared tumor characteristics, treatment patterns, and survival between patients with high *versus* low familial risk of breast cancer.

Results, recommendations, and benefit to patients

Compared to patients at low familial risk (n=575), those at high familial risk (n=58) were not more frequently detected by screening nor detected at an earlier stage. High-familial-risk patients received systemic therapy significantly more often, especially for node-negative or receptor-positive disease. Five-year disease-specific survival rates of patients at high *versus* low familial risk were 86% and 90%, respectively. After adjustment for other prognostic variables, there was no difference in breast cancer mortality in general. A strong family history was, however, associated with a nonsignificant increased breast cancer mortality risk in patients ≤ 40 years of age and in patients treated without chemotherapy.

Based on this study, we conclude that there is a need for guidelines on the screening and management of young women at high familial risk. By better informing the public and primary-care physicians, it should be possible to increase the number of women identified as high risk for breast cancer and to propose specific prevention protocols. Additional research is required to confirm whether a strong family history of breast cancer impairs survival of very young patients and those treated without chemotherapy.

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Langewitz Wolf | Evaluation of the Swiss Cancer League communication skills program for clinical oncologists and oncology nurses (OCS 01185-09-2001)

Introduction

A total of 70 nurses and 62 oncologists providing 258 interviews on video participated in the Swiss Cancer League communication skills training program consisting of a 2.5 days initial workshop, a half day follow-up workshop, and up to five feedback units by telephone. The videotapes recorded interviews with simulated patients that were conducted prior to the intervention and at the follow-up workshop. Participation was voluntary for oncology nurses and mandatory for oncologists, who needed the course for their board certificate.

Methods

Interviews were analyzed with the Roter Interaction Analysis System (RIAS): RIAS yields categories under which patient and professional utterances can be summarized. Furthermore, it allows reporting on the emotional climate of an interview using global ratings. Global ratings could be grouped into three factors: negative emotionality of the interaction, positive affect in the medical professional, and positive affect in the patient (29%, 13%, and 11% explained variance). German and French interviews were also analyzed using an instrument called OPTION (observing patient involvement scale), which assesses the extent to which professionals involve patients in decision-making. To detect specific intervention effects in terms of patient-centered communication, further variables were calculated based upon RIAS data. These include the identification of segments in the interview (reciprocities) when professional and patient communicate in an intertwined way (e.g., the patient provides a concern or psychosocial information – the professional reacts with an appropriate statement; target sequences). Pre- and postintervention interviews were compared using ANOVA statistics, or by calculating the difference between pre- and postintervention means (paired t-test).

Results

A total of 54,692 utterances were analyzed from 34 Italian-speaking, 160 German-speaking, and 64 French-speaking professionals and their respective simulated patients. The largest part of the interviews consists of the exchange of information: 36,677 utterances can be summarized under this category.

In nurses there is a significant increase in the proportion of empathic statements (1.6 versus 3.2%), of reassuring statements (2.3 versus 3.4%), a decrease in medical information given (17.8 to 13.3%), an increase in closed and open questions concerning psychosocial information (2.8 versus 4.0%), a decrease in medical information provided by the patient, and an increase in lifestyle information given (8.1 versus 6.7%; 3.3 versus 5.7%). In oncologists there is an increase in checking/summarizing utterances (1.8 versus 2.3%) and an increase in patients' explicit agreement statements (3.6 versus 4.7%). In nurses there are several significant changes, indicating that after the intervention nurses and their patients talk more about psychosocial issues and less about medical/therapeutic issues (28.1 versus 33.2%; 30.6 versus 21.7%). Again in nurses, there is a significant training effect on the length of time patients can speak without being interrupted by the professional: 3.7 versus 4.3 utterances. No such effect could be observed in oncologists (2.8 versus 2.9 utterances).

The analysis of reciprocities shows a decrease in the patients' reactions to the provision of information from the physician (11.6 to 7.8% of target sequences) concerning providing or asking for further information and an increase in the number of responses on an psycho-emotional level (10.0 to 11.7% of target sequences). When given the opportunity to bring in his/her position, patients react with more emotional statements to nurses and less emotional statements to physicians (12.3 to 17.7% versus 15.9 to 11.5%). In talking with physicians, patients increase the number of statements displaying congruence (23.3 versus 28.8%). With nurses the number of true empathic responses increases from 14.2 to 18.5%, whereas the number of statements showing understanding/congruence decreases from 35 to 30%.

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Stiefel Frédéric | Development of an adequate method to assess meaning in life of cancer patients with advanced disease (OCS 01585-08-2004)

Quality of life of cancer patients not only depends on their physical state but to an important extent also on psychological factors. Among these factors, finding meaning in life can be regarded as a key element; finding meaning in their lives seems to provide protection to persons who are facing traumatic events. On the contrary, absence of a perception of the meaning of life in cancer patients with advanced disease is often associated with a desire for death or a request for euthanasia. The concept of meaning in life – which has long interested thinkers and psychotherapists – has become a central element of brief

psychotherapeutic interventions in cancer patients with advanced disease. Despite these developments, a major obstacle hampers scientific investigation of this concept: the lack of an adequate method to measure the individual's sense of meaning in life.

Aims of the study

This study aims to develop a qualitative and quantitative instrument evaluating meaning in life of cancer patients (SMiLE). The study is part of a multicenter project involving centers in Lausanne, Munich, and Dublin.

Methods

The instrument is based on the method that was utilized to develop the SEIQoL (Schedule for the Evaluation of Individual Quality of Life). Patients are asked to co-construct the instrument with the investigators by answering the question, "What provides meaning in life?" and then defining a maximum of five domains that provide or could provide meaning in life in their current situation; following this, patients indicate their degree of satisfaction with the defined domains and weigh the importance of each domain. The method is based on an individualized, qualitative, and quantitative approach.

Results

One hundred cancer patients were included in this study in Lausanne and compared with a representative sample of the general population (N=856). The family is the domain perceived as the most important in providing meaning in life in cancer patients and the general population. However, cancer patients then favor "spirituality" and "nature" in contrast to the general population, which rates the domains "work" and "economic situation" as the second most important domains. Despite the fact that cancer patients suffer from a serious disease and undergo heavy treatments, the results of SMiLE are surprisingly high, as is the cancer patients' satisfaction with health. This can be explained by a constant change in expectation during the course of disease. This study has contributed to evaluation of the feasibility, acceptability, and validity of this new instrument, the SMiLE.

Benefits to patients

Meaning in life is an important concept for understanding patients suffering from serious or advanced diseases. This topic was already approached by Victor Frankel, who based his concept on his painful experiences during the Second World War and utilized it for psychotherapeutic interventions. Interest has grown recently in Frankel's approach for use in psycho-oncological interventions. A reliable and valid instrument measuring meaning in life is therefore the first step in its scientific investigation. The measure could become very useful for the development and evaluation of psychotherapeutic interventions focusing on meaning in life with cancer patients.

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Further research projects completed in 2004 and 2005

PD Dr. phil. Jürg Bernhard | KLS 01116-02-2001 | CHF 123,075.–

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Reframing of perception in patients with lung cancer experiencing recurrence: Does it play a role for quality of life and utility evaluation? A prospective longitudinal cohort study

Prof. Alexander Kiss | NPK 01249-04-2002 | CHF 84,100.–

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Patient preferences vs. physician perceptions of treatment decisions in cancer therapy

D' med. Daniele Stagno | NPK 01209-07-2001 | CHF 180,000.–

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RCT (Randomized Clinical Trial) of the treatment of adjustment disorders with anxious and depressed mood in patients with cancer (Switzerland)

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Completed research projects already presented in 2004 edition

These projects can be found at www.swisscancer.ch/research

(Text in German and French only)

PD Dr. phil. Jürg Bernhard | OCS 01165-09-2001 | CHF 268,481.–

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Communication about clinical trials and treatment options: A randomized controlled trial of a consultation skills training package

Dr. phil. Daniel Gredig | KLS 01227-02-2002 | CHF 50,000.–

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