

# ANNUAL REPORT 2013

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## ISREC FOUNDATION

A FOUNDATION SUPPORTING  
CANCER RESEARCH  
LINKING SCIENTISTS  
IN FUNDAMENTAL RESEARCH  
WITH CLINICIANS  
AND ENCOURAGING SCIENTIFIC  
TRAINING IN SWITZERLAND

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## EDITORIAL

# JUBILEE YEAR

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### PREFACE FROM THE PRESIDENT OF THE FOUNDATION COUNCIL

The ISREC Foundation and Institute entered in June 2013 their fiftieth year of activities in the service of cancer research. This jubilee crowns a constant commitment to overcome cancer, a disease that still today remains a major challenge for society.

We wish a warm welcome to two new members. In May, Mrs. Martine Brunschwigg-Graf joined our Foundation Council and in August, Prof. Francis -Luc Perret took over the management of the Foundation.

In September, the Foundation moved onto the CHUV campus, coming thus nearer to the future AGORA - Cancer Center. This major project, in which the Foundation is involved as Project Manager "Maître d'ouvrage" remains our priority. AGORA will be a key building in the new Swiss Cancer Center. From 2017 onwards it will accommodate more than 300 scientists occupying an area of 12,000 m<sup>2</sup>. Dedicated to translational research, it will aim to gather interdisciplinary teams of physicians, biologists, immunologists, bioinformaticians and bioengineers from the different partner institutions. The numerous and constant interactions among these teams will accelerate the development of new therapies for the benefit of patients.

In addition to the funds allocated to translational research, scientific education benefited, as every year, from our support. Grants were awarded to students of the UNIL/EPFL summer program as well as to PhD students participating in the programs "Molecular life sciences" (EPFL) and "Cancer and Immunology" ( UNIL). The work that these young people will perform as they prepare their theses will help toward understanding the mechanisms of cancer cells and will allow the identification of new therapeutic targets, in particular for lymphoma, glioblastoma, leukemia, melanoma, sarcoma and lung cancer.

The challenges to overcoming cancer are still numerous. Today, as yesterday, to continue its mission the ISREC Foundation needs each one of you. In conclusion, I would like to thank you for your confidence and your support. Your commitment to our cause is of the utmost value and remains indispensable to the fulfillment of our projects.

Yves J. Paternot

## CANCER RESEARCH

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### CANCER FACTS AND FIGURES

There exist more than a hundred types of cancer as all the tissues of an organism can be affected and for certain tissues, several types of cancer are possible. Cancer is the 2nd cause of mortality in Switzerland, after cardio-vascular disease.

In Switzerland, about 37'000 new cases are registered each year (estimate for 2010 of the National Institute for Cancer Epidemiology and Registration – NICER, 2013).

More than 100'000 people live with a cancer diagnosed since less than 5 years (prevalence). (Source: Globocan 2002).

Today in Switzerland, four out of ten people (one man out of two and one woman out of three approx.) develop cancer during their life time, and unfortunately the disease can be cured in only half of the cases.

The risk of having a cancer before 70 years old is approximately 25% for men and 20% for women (Sources: FSO, NICER, 2012).

For all types of cancers, relative survival after 5 years is estimated in Switzerland at 48% for men and 57% for women (Source: EURO CARE 4; based on data of 7 cantonal registers).

### VERY ENCOURAGING RESULTS

Even though the number of cancer cases increased during the last two decades (in particular because of early diagnosis and the ageing of the population), there has been a noticeable decrease in death rates for cancer overall (- 27.9 % between 1992 and 2011).

In women, the most frequent cancer (responsible for death in 2011) is breast cancer followed by lung cancer and then by colon and rectum cancer. At diagnosis (incidence 2010) 1) breast, 2) colon and rectum, 3) lung, 4) melanoma. (Sources: FSO, NICER, 2013).

In men, the most frequent cancer (responsible for death in 2011) is lung cancer, followed by prostate cancer and then by colon and rectum cancer. At diagnosis (incidence 2010) 1) prostate, 2) lung, 3) colon and rectum and 4) melanoma. (Sources: FSO, NICER, 2013).

Several of the most frequent cancer types have regressed in Switzerland since end of the 1980's. Among these types of tumors are the colon and rectum as well as the stomach in both sexes (these are cancer types which are related in particular to lifestyle) and female breast cancer, which has decreased thanks to clearly improved therapies and early detection.

It has however to be noted that lung cancer has notably increased among women, consequence of the rising number of smokers in young generations whereas it decreased by men.

Although cancer mortality is decreasing, the disease is unlikely to disappear completely. Therefore the objective in the long term is rather to transform it into a chronic disease, which it will be possible to control and/or cure.

Note that in 1990, there were approximately 140'000 living people in Switzerland, for whom a cancer diagnosis had been made ("cancer survivors"). This number has since increased steadily and in 2010 they were almost 300'000 (Source: Oncosuisse).

# CANCER RESEARCH

## EVOLUTION OF CANCER DEATH IN SWITZERLAND (1992-2011)

Deaths 2011		Age-standardized rates*/ 100'000 inhabitants Difference (%) 1992-2011	
<b>All cancers</b>	<b>16462</b>	-27.9	
Lung, bronchi (females)	1150		54.8
Liver, bile duct	632		7.7
Brain	514		4.0
Pancreas	1119	-3.1	
Esophagus	454	-4.8	
Melanoma	306	-10.3	
Colon and rectum	1767	-29.6	
Bladder	553	-31.7	
Uterus corpus, ovary, adnexa	673	-32.0	
Multiple myeloma	293	-34.3	
Lung, bronchi (males)	2035	-38.1	
Breast (females)	1371	-38.3	
Prostate	1366	-38.9	
Larynx (males)	83	-46.7	
Stomach	536	-53.1	
Uterus, Cervix	91	-57.1	
Testis	13	-62.5	
Hodgkin's disease	19	-75.0	

-90.0 -70.0 -50.0 -30.0 -10.0 10.0 30.0 50.0 70.0 90.0

\* European standard population  
Source: Swiss Federal Statistical Office, Neuchâtel

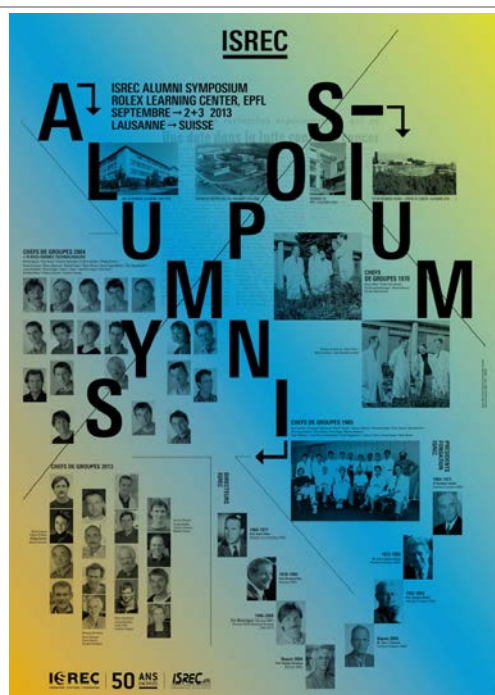
## HIGHLIGHTS 2013

### EVENTS SUPPORTED BY THE ISREC FOUNDATION IN 2013

#### Gordon research conferences - Stem cells and cancer

**April 21-26, 2013, Les Diablerets, Switzerland**

This conference presented cutting-edge research on the molecular, cellular and genetic mechanisms controlling self-renewal and differentiation of both normal and cancer stem cells. The conference was organized by Prof. Andreas Trumpp (Heidelberg) and Prof. Len Zon (Boston). More than 140 participants discussed with 26 internationally recognized speakers and leaders in their field the most exciting and novel unpublished data dealing with cancer stem cells and their role in cancer development, progression and metastasis. The conference received outstanding reviews and will be repeated in 2015 in California before returning to Les Diablerets in 2017.



#### Alumni Symposium

**September 2 - 3 2013 – Rolex Learning Center, EPFL, Lausanne**

This symposium, which brought together more than 300 researchers and scientists who are or have been part of the ISREC (Swiss Institute for Experimental Cancer Research), including two Nobel Prize-winners, was a great success. Marking the start of the celebrations for the 50th anniversary of the ISREC Foundation and of the Institute ISREC@EPFL, this special event helped provide a reflection, not only on the research done, but also on the incisive future projects in the fight against cancer, including the AGORA project. Held over two days, a series of conferences addressed topics including the control of cell division, cell proliferation and stem cells.

### EVENTS ORGANIZED IN FAVOUR OF THE ISREC FOUNDATION IN 2013

#### Brunch Institute Florimont, Geneva

Event organized on June 1<sup>st</sup>, 2013 by the parents of students of the Institute Florimont to raise money for cancer research. Further to the brunch, CHF 3'300.- could be donated to our Foundation.

#### AGO Trophy, Lonay

Fifty volunteers prepared the third edition of this trophy in memory of their friend Agostino who died from cancer. Nearly 500 people came and participated in the various activities and tournaments organized in Lonay on June 30, 2013. The success of this event made it possible for the organizers to give CHF 9'000.- to the ISREC Foundation.

#### “Corcelles-le-Jorat” Motorbike race

Since 1998, the committee of Team Girard has been bringing together owners, riders and lovers of old motorbikes, organizing every year an event for old-timers and donating half of the profits to the ISREC Foundation. After the sixteenth edition of the running which was held on August 24-25, 2013 in Corcelles-le-Jorat, they could donate CHF 1'000.-.

## AGORA – CANCER CENTER

### ISREC FOUNDATION, PROJECT MANAGER (“Maître d’ouvrage”)

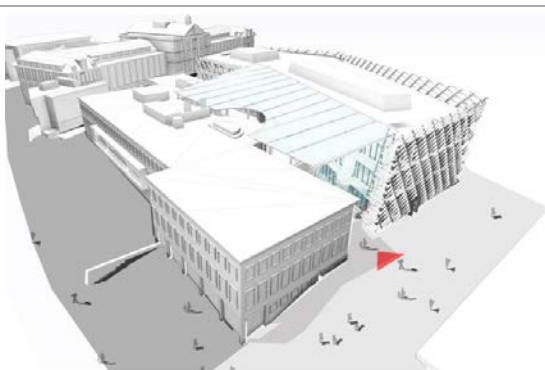
Located on the CHUV site, the future AGORA - Cancer Center, will be the key component of the new Swiss Cancer Center, whose governance will be jointly provided by the CHUV, UNIL, EPFL and the ISREC Foundation. It will be the place where fundamental and clinical research meet to find solutions to the many challenges posed by cancer. It will also host researchers and clinicians from other institutions, including the HUG.



Architectural project of the winner: Behnisch Architekten, Stuttgart

### Project

Among the twenty-two projects received and evaluated, a team of experts selected, in the first phase, eight candidates. Four architectural offices were then tasked with developing a detailed project. The team of experts finally unanimously selected in January 2013 the architects Behnisch as winner.



Atrium: exterior



interior

### Calendar

April 2014:	Submission of application for building permit
May 2014:	Open call for offers for the construction of the building as General Contractor
August 2014:	Award of the construction contract
September 2014:	Finalizing of the agreement of General Contractor
October 2014:	Starting the building work, subject to obtaining planning permission
February 2017:	Commissioning of the AGORA building

## SUPPORTED PROJECTS

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### SUMMER RESEARCH PROGRAM (SRP)

This year again, the ISREC foundation supported during 8 weeks (from July 4 to August 28, 2013) the training course in laboratories doing cancer research of six students from the EPFL and five students from the UNIL/CHUV.

This first contact with a research environment represents for these young biologists or doctors a very enriching experience and an opportunity of creating new links on an international level. At the end of this program the occasion was given to them to present their work during a mini symposium which was organized on the EPFL campus on August 27, 2013.



Photo: Combined EPFL and UNIL Summer Research Program participants at students' symposium 2013



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## SRP - TOPICS COVERED

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Shadrack Osei **Frimpong**

**Group Prof. Didier Trono – EPFL/SV/GHI**

Deciphering the kinetics of KRAB-ZFP-mediated repression and expression

*KRAB ZFP = Krüppel-associated box domain-zinc finger proteins*

Diane **Libert**

**Group Prof. Viesturs Simanis – EPFL/SV/ISREC**

Studying cell division in fission yeast

Vivian **Liu**

**Group Prof. Pierre Gönczy – EPFL/SV/ISREC**

Centriole inheritance and ectopic biogenesis

Aline **Marino do Nascimento**

**Group Prof. Liliane Michalik – UNIL/CIG**

Improving melanoma treatment: promising MEK inhibition in BRAF inhibitor-resistant cells

Ben **Mormann**

**Group Prof. Joachim Lingner – EPFL/SV/ISREC**

Characterization of human MRE11

Aparna **Pandey**

**Group Prof. David Gatfield – UNIL/CIG**

Regulation of circadian gene expression by microRNAs

Richard **Park**

**Group Prof. Yann Barrandon – UNIL/CHUV**

Characterization of skin from SPINK5 knockout mice

*SPINK5 = serine peptidase inhibitor, Kazal type 5*

Rouhallah **Ramezanifard**

**Group Prof. Melody Swartz – EPFL/SV/IBI**

In vitro investigation of VEGF-A and VEGF-C -mediated HDF activation and cancer cell invasion

HDF = Human dermal fibroblast

VEGF = vascular endothelial growth factor

Lara **Seidman**

**Group Prof. Winship Herr – UNIL/CIG**

The role of HCF-1 in liver development

*HCF = host cell factor*

Hélène **Tubeuf**

**Group Prof. Nicolas Mermod – UNIL/Institute of biotechnology**

Polyadenylation and expression of a transgene under the control of an RNA polymerase I promoter in transposition

Florence **Winteler**

**Group Prof. Yann Barrandon – EPFL/SV/IBI**

Characterization of rat embryonic thymic epithelial cells

## GRANTS

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### “ALLOCATED GRANTS”

The “allocated grants” are awarded to the best PhD students taking part in doctoral programs in biology or medicine.

The ISREC Foundation receives a donation from a physical or moral person and is guarantor of the use of the full amount for the specific project. The Foundation controls the management of the grant.

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#### GRANT “RICHARD AND RITA BARMÉ”

##### **Function of telomeres and their molecular composition**

This “allocated grant” amounting to CHF 80'000.- per year was awarded to Larissa Grolimund in October 2008 for 48 months.

**Larissa Grolimund** is working in the group of Prof. Joachim Lingner (EPFL/SV/ISREC).

##### **Project description**

Telomeres protect the linear ends of eukaryotic chromosomes by preventing chromosomal end-to-end fusions and telomere attrition. They consist of repetitive DNA sequences, telomeric repeat-containing RNA (TERRA) and proteins. Telomeres play a crucial role in chromosome stability and cancer biology. With each cell division, telomeres shorten, as the replication machinery of the cell is not capable of fully copying the very terminal part of chromosomes. Therefore, after a certain number of cell divisions, telomeres become critically short and elicit signals in order to stop the proliferation. A cell can circumvent the signal for critically short telomeres by activating mechanisms that elongate telomeres. Mostly, telomere elongation is effected by the expression of the telomerase enzyme. In this case, cells gain the ability to divide indefinitely, which can eventually lead to the formation of cancer. In our laboratory, we are focusing on the identification of molecular mechanisms that regulate and control telomere length and function in normal cells and cancer cells. We aim at developing a new methodology that allows the identification of proteins that are present at telomeres. Importantly, the technique should allow us to determine variations between protein compositions of telomeres from different cells such as normal cells and tumor cells. In this context, the study will provide useful information to understand the role and regulation of telomeres in normal and, more importantly, in cancer cells. Prospectively, the discovery of novel telomeric proteins may identify new targets for cancer therapies.

Until now, the complete molecular composition of telomeres has not been described and it has remained enigmatic how the telomeric protein composition (telosome) changes during various states such as during the cell cycle, in order to regulate telomerase, or upon telomere shortening to induce cellular senescence.

##### **Final report: Quantitative telosome isolation protocol (Q-TIP): elucidation of telomere composition in various cell states**

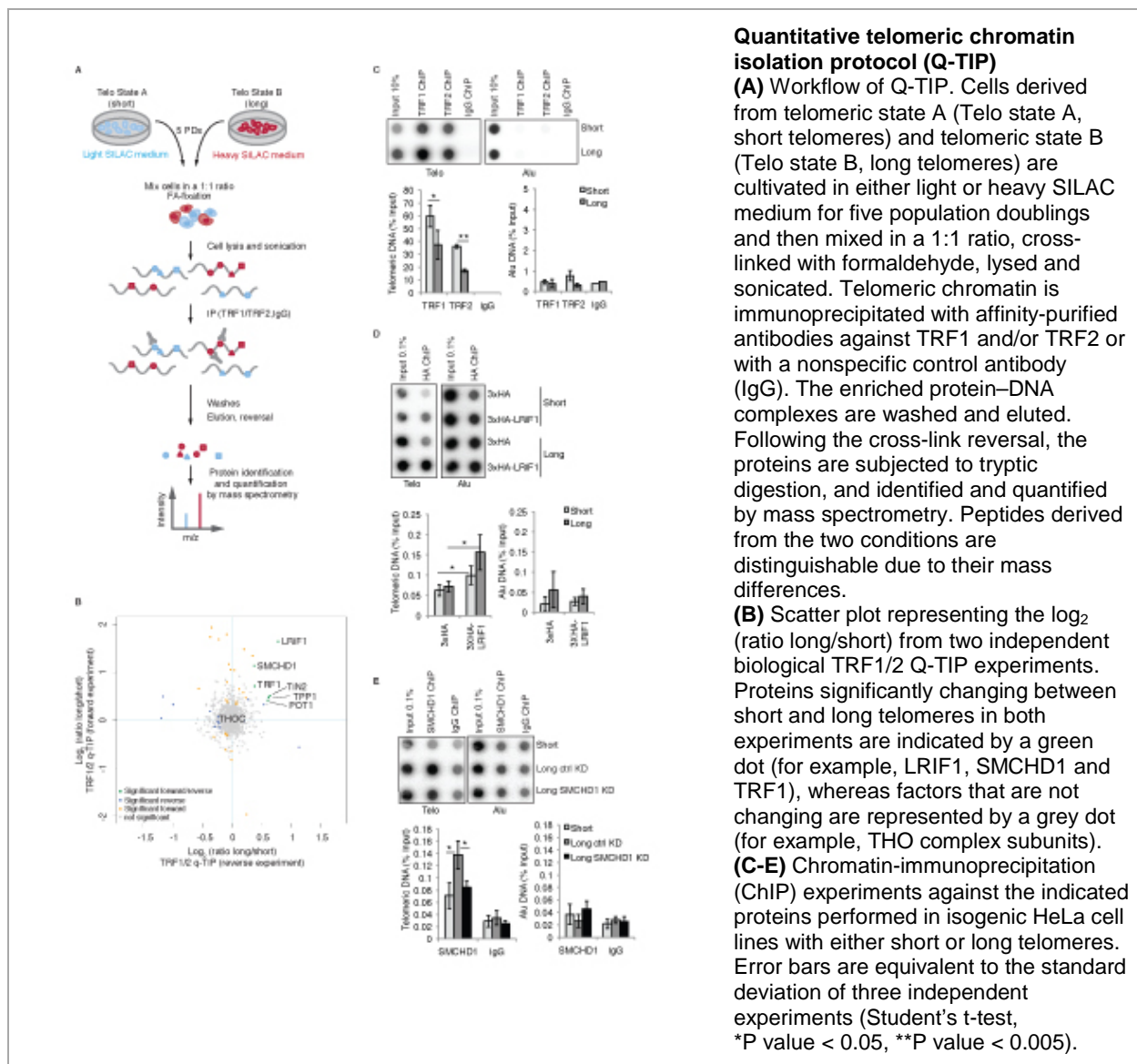
We have established a quantitative telomeric isolation protocol (q-TIP) that enables the determination of telomeric protein composition. In this method, chromatin is chemically cross linked and telomeric chromatin is purified with antibodies against TRF1 and TRF2, two telomere-specific factors. Q-TIP also involves the use of SILAC (stable isotope labeling of amino acids in cell culture) based mass spectrometry which allows the quantitative comparison of telomeric chromatin compositions obtained from different telomeric states. With q-TIP, we specifically enrich for telomeric DNA and associated proteins, as confirmed by the detection of the telomere-specific shelterin complex and other known telomere components. We have applied q-TIP to human cancer cells with long and short telomeres and we can observe quantitative differences in the protein composition between these states.

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## ...> ACADEMIC TRAINING

Importantly, we have validated these differences with complementary techniques. Moreover, we have discovered novel telomeric factors, of which some preferentially bind to long telomeres. Notably, we have used complementary techniques to verify the presence at telomeres of a subset of the newly identified telomeric proteins, including SMCHD1, LRIF1 and the THO complex. Strikingly, the telomeric chromatin composition shows significant changes upon depletion of one of the newly discovered factors, SMCHD1, indicating its importance at telomeres.

In summary, q-TIP enables the identification of novel telomeric proteins and the elucidation of protein composition variations at telomeres under different cellular conditions.



## GRANTS

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### “ISREC GRANTS”

The “ISREC grants” or financial supports from the ISREC Foundation for a thesis are awarded to the best PhD students taking part in doctoral programs in biology or medicine.

These grants amounting to CHF 80'000.- per year are awarded for four years. They are financed by donations and legacies.

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### GRANT “MOLECULAR BIOLOGY OF CANCER AND INFECTION” Identification of *Hes1* target genes in murine and human T-ALL

This “ISREC grant” amounting to CHF 80'000.- per year was awarded to Silvia Wirth in September 2009 for four years.

[Silvia Wirth](#) is working in the group of Prof. Freddy Radtke (EPFL/SV/ISREC).

#### Project Description

T cell acute lymphoblastic leukemia (T-ALL) is the most common hematopoietic malignancy in children. Improved chemotherapy cures 80% of T-ALL patients. However, patients who relapse have poor prognosis. It is therefore important to understand the molecular pathways that control disease development in order to be able to improve treatment of relapse patients. Eighteen years ago, a chromosomal translocation that results in constitutive activation of the Notch1 signaling cascade was identified in a small cohort of T-ALL patients, suggesting a link between aberrant NOTCH1 signaling and T-ALL. Subsequently, in 2004, a landmark study demonstrated that the majority (>50%) of all T-ALL patients carry activating point mutations in NOTCH1 and that NOTCH1 signaling is indeed causative of T-ALL. These findings therefore identify NOTCH1 as a key molecular mediator of T-ALL pathogenesis.

Active NOTCH1 signaling in T cells leads to the expression of a myriad of genes, including the transcriptional repressor *Hes1*. We have therefore studied the role of *Hes1* in a variety of mouse models of T-ALL that mimic the human disease. The aim of this study was to evaluate whether *Hes1* affects disease development and maintenance and to characterize its function as a transcriptional repressor in T-ALL.

#### Final report

T-ALL can be modeled in the mouse by expressing the constitutively active Notch1 intracellular domain (NICD) in T cell progenitors. This can be achieved either by the use of tissue-specific promoters or via retroviral expression in hematopoietic stem cells. It is possible to distinguish between an early and a late stage of the disease in the retroviral model (1). Using the retroviral model, we show that *Hes1* is not required in established, late stage T-ALL cells, but that it promotes the establishment and progression of the early stages of the disease.

Therefore, we set out to systematically delineate the gene regulatory networks downstream of *Hes1* by combining RNA-seq and ChIP-seq in WT and *Hes1* knockout NICD-dependent T-ALL. The Figure shows a typical ChIP-seq binding profile of *Hes1* on its own promoter. When we compare the gene expression of cells in the presence and absence of *Hes1* by RNA-seq, we find 1268 differentially expressed genes. Of these, 1193 are up-regulated upon loss of *Hes1*, and thus may represent direct targets, assuming *Hes1* functions as a transcriptional repressor. In addition, 75 genes show reduced expression and thus may be regulated by indirect mechanisms. Surprisingly, putative direct target genes are not significantly associated with any gene ontology (GO) category.

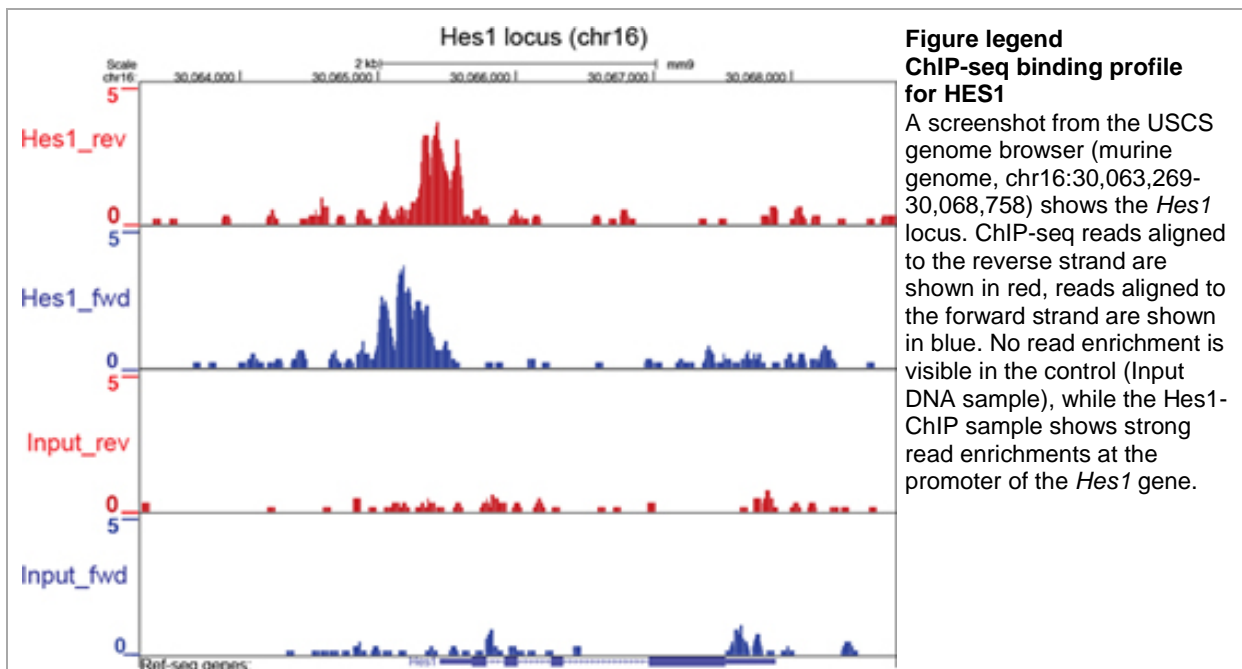
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## ...> ACADEMIC TRAINING

However, indirect targets can be assigned to five significant GO categories, including regulation of transcription, cell division and DNA repair. ChIP-seq analysis has identified 37 genes that interact directly with Hes1; by combining these results with the gene expression data, we aim to identify both direct and indirect targets of Hes1 that promote T-ALL.

We have also investigated the function of HES1 in human T-ALL and can show that the overexpression of dominant negative versions of HES1 in two patient-derived cell lines (T-ALL1, CUTLL-1) does not affect proliferation or apoptosis, underlining that *Hes1* does not affect cell viability once cells are fully transformed to the leukemic state.

Our results indicate that *Hes1* is dispensable for the maintenance of murine and human NICD-induced T-ALL. However, the role of Hes1 in promoting the early stages of the disease appears to be highly complex and is likely to involve both direct and indirect control of gene regulatory networks.



### Reference

- Li, X., Gounari, F., Protopopov, A., Khazaie, K., von Boehmer, H. (2008). Oncogenesis of T-ALL and nonmalignant consequences of overexpressing intracellular NOTCH1. *J. Exp. Med.* 205, 2851-2861.

## GRANTS

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### GRANT "CANCER AND IMMUNOLOGY"

#### **Role of mesenchymal Notch signaling in melanoma development and progression**

This "ISREC grant" amounting to CHF 40'000.- per year was awarded to Elena Menietti in June 2011 for four years.

**Elena Menietti** is working in the group of Prof. Gian-Paolo Dotto (Department of Biochemistry, UNIL).

#### **Introduction**

The aim of the project is to test whether alterations in cell-cell communication resulting from down-modulation of Notch signaling may play a role in skin cancer development.

The original proposal, as suggested by the title, was focused on melanoma. However, the role of Notch signaling in this context is poorly understood and for this reason we decided to switch our focus to squamous cell carcinoma, one of the most frequent types of solid human tumors, in which the tumor suppression function of Notch is now well established.

It has been shown that the tumor microenvironment exerts a huge effect on cancer onset and development, driving cancer research to a more complicated level, in which not only pathways within the cells are important, but also the relationship of these particular cells with the surrounding cells and the environment; for example, the tumor stroma has been found to host chronically activated fibroblasts, so called "cancer-associated fibroblasts" (CAFs) which, in contrast to normal fibroblasts, have a demonstrated ability to enhance tumorigenesis and/or invasiveness of cancer cells, forming an appropriate niche for cancer development. CAFs are capable of interacting with the tumor through the production of various kinds of diffusible factors, and maybe also by cell-cell contact interactions.

Our assumption is that normal stroma and epithelial cells can also interact with the tumor, eventually mitigating its aggressiveness.

Notch signaling is very important for intercellular communication and it is highly context-dependent. It may act as a tumor suppressor, for example in keratinocytes, or as an oncogene, as is likely to be the case in melanocytes.

Some experiments have shown that in the mesenchymal compartment the loss of Notch signaling is capable of inducing a CAF phenotype.

#### **Results after the first year**

In the first year we initially performed some in vivo experiments, which showed that the injection of cancer cells with normal cells, both epithelial and mesenchymal, gives rise to less aggressive tumors.

Then, to investigate whether our reference pathways are involved, we developed a system to induce p53 and Notch signaling in cells.

We have performed several experiments of co-culture between cancer cells and the same cells in which we induced p53 or Notch signaling. Preliminary results show that the co-culture with cells in which p53 has been induced results in an increase in the proliferation of cancer cells, while the co-culture with cells in which Notch has been induced induces growth arrest in cancer cells. The induction of either p53 or Notch in the tumor cells induces growth arrest, but the effect on neighboring cells is strikingly different.

#### **Results after the second year**

The skin presents many differences among human populations: besides pigmentation differences, which rely on the presence of polymorphisms in the pigmentation-related genes, there are other physiological differences in skin structure, the genetic background of which is not yet understood. For example, cellular and biochemical composition differences in the outer layers of the epidermis exist between African and Caucasian/Asian populations.

## ...> ACADEMIC TRAINING

From a pathologic point of view, the differences among the populations are interesting. The predisposition to skin cancer (basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma) is much higher in Caucasians than in other populations.

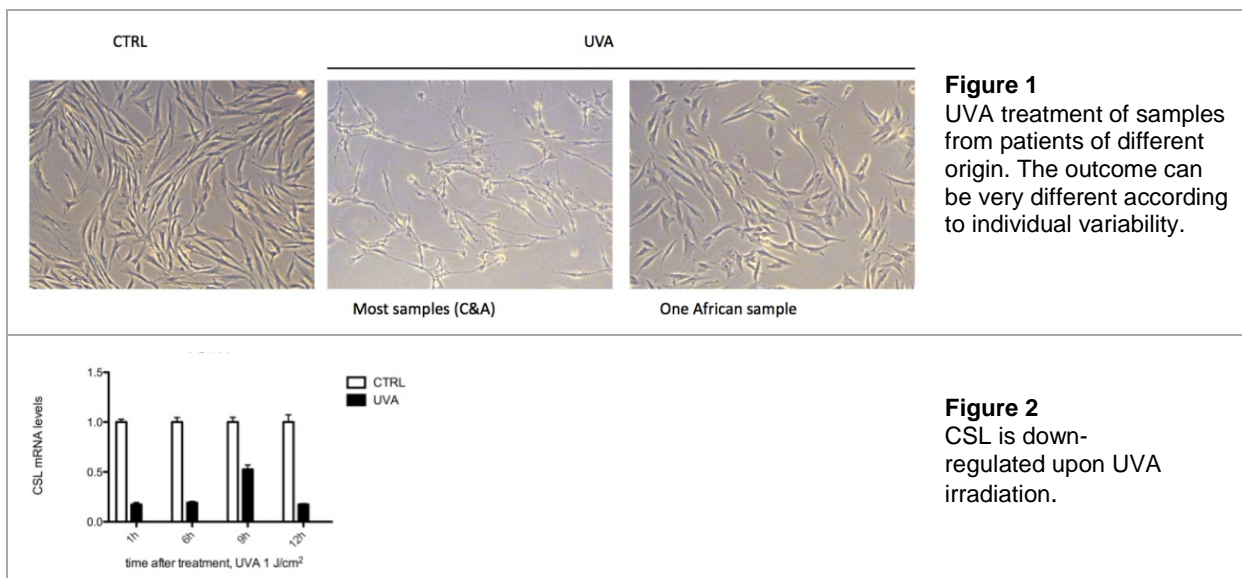
The major risk factors for the occurrence of skin cancers differ between populations: for example, the major risk factor for the Caucasian population is UVA exposure, while for the African population it is the presence of hypertrophic scars or keloids.

Since both UVA exposure and wound healing potently activate fibroblasts, and the presence of activated fibroblasts, or CAFs, has been associated with the occurrence and persistence of skin cancer, we have hypothesized that common pathways may be involved in fibroblast activation in response to the different stresses and subsequent cancer onset.

During the second year of this project, we focused on the role of the Notch-CSL pathway in CAF transformation. We have already demonstrated that CSL is suppressed in response to UVA exposure. We are now investigating the response of primary human dermal fibroblasts to different stimuli which mimic oxidative stress, fibrosis and UVA exposure itself, trying to understand: 1) the modulation of CSL in response to the different stimuli, and 2) the molecular pathways which are responsible for this modulation.

We have also found some genetic differences between populations in the CSL locus. These seem to be directly linked to different abilities to modulate CSL expression by different transcription factors, and we are currently investigating whether cells from different populations may have a different response to UVA irradiation.

Until now, we have demonstrated that CSL is downregulated after both UVA irradiation and exposure to pro-fibroblastic signals. We are now investigating the upstream pathways linking these stimuli to CSL downmodulation, in order to understand whether acting on these upstream pathways could be useful for skin cancer prevention, by modifying the response of mesenchymal cells to stress.



## GRANTS

### GRANT "CANCER AND IMMUNOLOGY"

#### The role of the Notch receptor in CD4 T<sub>H</sub>17 cell differentiation and its relevance in cancer

This "ISREC grant" amounting to CHF 40'000.- per year was awarded to Manuel Coutaz in June 2011 for four years.

**Manuel Coutaz** is working in the group of Prof. Fabienne Tacchini-Cottier (Department of Biochemistry, UNIL).

#### Introduction

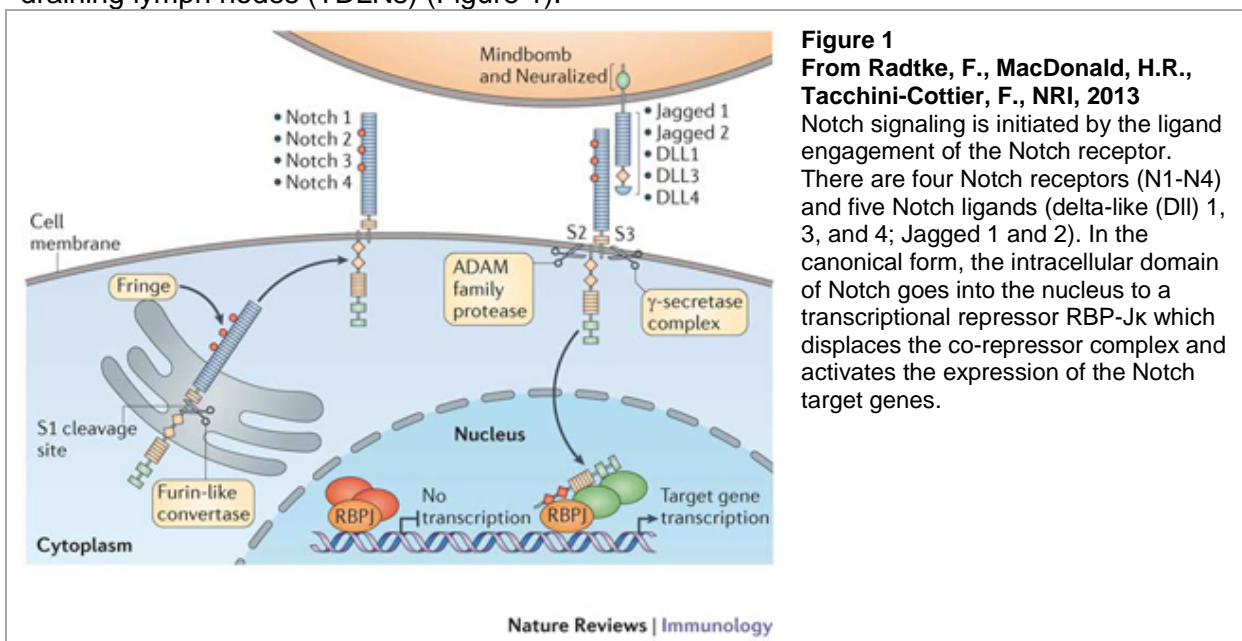
We are currently investigating the role of Notch1 and Notch2 expression in T<sub>H</sub>17 cell differentiation and in the generation of a T<sub>H</sub>17 response in the tumor microenvironment. The function of T<sub>H</sub>17 cells in cancer appears to be context-dependent, and was shown to either promote or reduce tumor growth.

The role of Notch receptor signaling in T<sub>H</sub>17 cell differentiation will be investigated *in vivo* using the murine experimental model of B16 melanoma cells. In this model, the IL-17 secreted by T<sub>H</sub>17 cells has been reported to influence tumor growth. Mice carrying a specific T-cell ablation of Notch1 and Notch2 or of the Notch transcriptional repressor RBP-Jκ will be injected with B16 melanoma cells to identify a role for Notch receptor signaling in the T<sub>H</sub>17 cell differentiation and tumor development.

#### Results after the second year

We first performed experiments to analyze the role of Notch receptors in T<sub>H</sub>17 cell differentiation *in vitro*. The absence of Notch1 and Notch2 on T cells appeared to be dispensable in T<sub>H</sub>17 cell differentiation. This lack of impact may result from the strong T<sub>H</sub>17-polarizing conditions used *in vitro* which could bypass the requirement of Notch receptor signaling.

To investigate a potential role for Notch receptor signaling in T<sub>H</sub>17 cell differentiation *in vivo*, mice deficient in Notch1 and Notch2 in their T cells (N1N2<sup>ΔCD4Cre</sup>) and their control (N1N2<sup>lox/lox</sup>) were injected with B16 melanoma cells. Tumor growth was evaluated for 15 days. A delay in tumor growth was observed in N1N2<sup>ΔCD4Cre</sup> mice. This correlated with an increase in intracellular levels of IL-17A and IFN-γ in CD4<sup>+</sup> T cells present in the tumor-draining lymph nodes (TDLNs) (Figure 1).



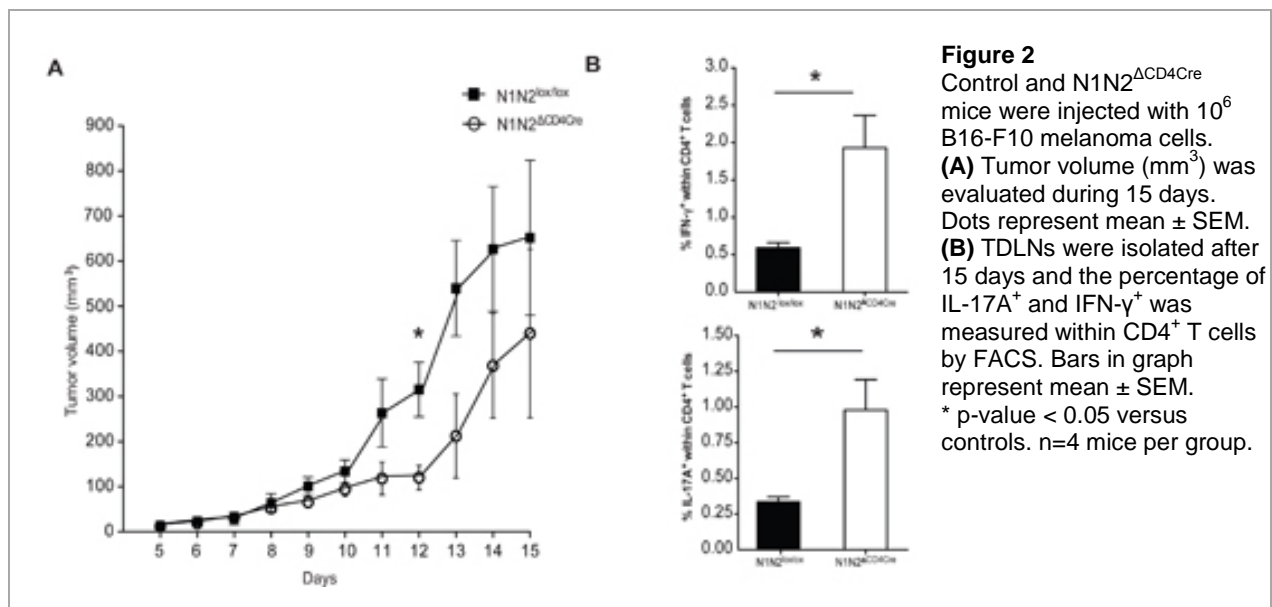


## ...> ACADEMIC TRAINING

To further investigate if Notch receptor signaling plays a role in other models of  $T_H17$  cell differentiation, we injected  $N1N2^{\Delta CD4Cre}$  mice and their controls with ovalbumin (OVA) in complete Freund adjuvant (CFA), an adjuvant reported to promote a strong  $T_H17$  cell differentiation. An increase in intracellular levels of IL-17A in  $CD4^+$  T cells was also observed in dLNs after 9 days. Interestingly, upon OVA restimulation *in vitro*, the secretion of IL-17A was strongly decreased in dLN cells of  $N1N2^{\Delta CD4Cre}$  compared to control mice. These results demonstrate a critical role for Notch receptor signaling in the regulation of  $T_H17$  cell differentiation. However, it remains to be investigated if IL-17A is secreted *in vivo* in the experimental melanoma model (Figure 2).

### Future directions

To further investigate how Notch receptor signaling influences IL-17A release, we will inject B16-OVA melanoma cells to evaluate the secretion of  $N1N2^{\Delta CD4Cre}$   $T_H17$  cells in TDLNs upon restimulation with OVA. We further want to investigate how the Notch receptor signaling impact on  $T_H17$  cell differentiation may affect the presence and function of Treg cells both in the TDLNs and in the tumor.



## GRANTS

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### GRANT "CANCER AND IMMUNOLOGY"

#### **Crosstalk between T lymphocytes and melanoma cells**

This "ISREC grant" amounting to CHF 40'000.- per year was awarded to Natalie Neubert in January 2012 for four years.

**Natalie Neubert** is working in the group of Prof. Daniel Speiser (Clinical Tumor Biology & Immunotherapy Group, LICR@UNIL).

#### **Introduction**

In 2008, over 67'000 new melanoma cases and over 14'000 deaths caused by this disease were reported in Europe, with the highest incidence in Switzerland. Despite considerable medical progress during the last few years, the prognosis of patients with metastatic melanoma remains poor.

Tumor-specific cytotoxic CD8+ T lymphocytes (CTLs) are the most important anti-tumor immune cells, because they can infiltrate the tumor microenvironment and destroy tumor cells. However, even after immunotherapy, the anti-tumor immune response usually does not lead to complete tumor eradication and tumors frequently relapse.

We are studying the crosstalk between CTLs and melanoma cells. To screen for important interactions between human melanoma-specific CTLs and melanoma cells, we have set up an autologous co-culture system of these two players. We are specifically interested in the implications for the surviving tumor cells.

A better understanding of the complex network of stimulatory and inhibitory interactions between tumor cells and host cells will likely help to identify novel target molecules, thus providing new options for anti-cancer therapy.

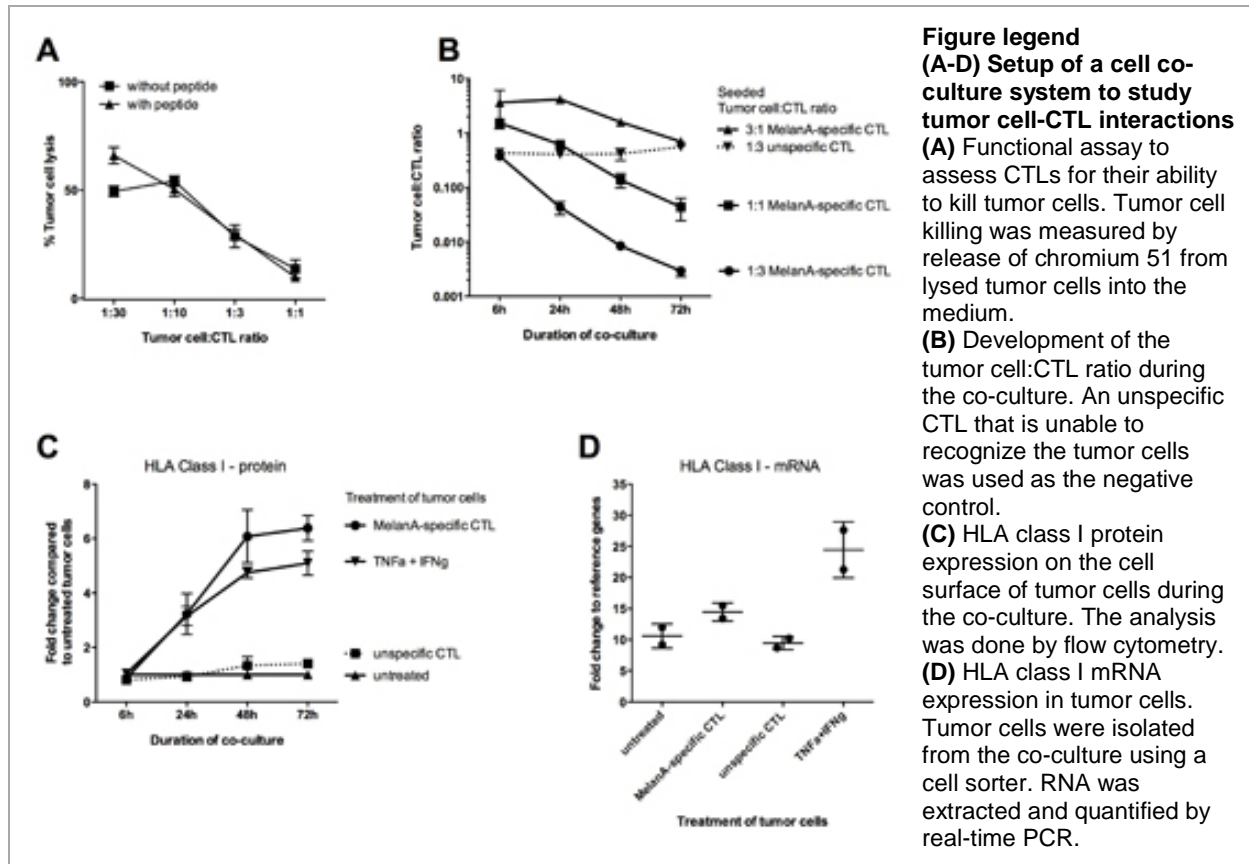
#### **Results after two years**

We have established co-cultures of four different melanoma patients. Previously, the tumor cell lines had been generated from metastasis- or tumor-infiltrated lymph node specimens. The tumor cell lines had been cultured for less than six months at the time of the co-culture. The CTLs were chosen based on their capacity to kill the autologous tumor cell line in a four-hour killing assay (Figure A). Different tumor cell:CTL ratios were seeded and analyzed at four time points between 6h and three days. The better the cytotoxicity of the CTLs (as determined in the killing assay), the more the tumor cell:CTL ratio decreased during the co-culture (Figure B).

In order to validate the co-culture system, the tumor cells that survived the co-culture were analyzed by flow cytometry. Non-target melanoma antigens such as chondroitin sulfate proteoglycan 4 (also called HMW-MAA) and membrane metallo-endopeptidase (also called CALLA) did not change during the co-culture. As expected, the target antigen MelanA decreased strongly, and HLA class I expression increased (Figure C). It is known that the CTL-derived cytokine IFN- $\gamma$  induces increased HLA Class I expression. PDL1, an inhibitory receptor ligand, also increases. PDL1 upregulation is a known mechanism of tumor escape from immune response.

Next, one time point and a given tumor cell:CTL ratio were chosen for differential gene expression analysis. Tumor cells were isolated from the co-culture using a cell sorter, and analyzed by quantitative PCR. In accordance with the protein expression, the mRNA levels for MelanA decreased and the mRNA levels for HLA Class I and PDL1 increased (Figure D). The melanocytic antigen PMEL (also known as gp100) also decreased. PMEL is regulated by the same transcription factor as MelanA.

## ...> ACADEMIC TRAINING



### Conclusion

We have set up an autologous co-culture system of human CTLs and tumor cells. The co-culture was validated through known changes at the protein level by flow cytometry and at the mRNA level by quantitative PCR.

We are currently establishing the methods to screen over 100 genes, with the aim to identify novel tumor escape mechanisms triggered in our co-cultures.

Our hypothesis is that CTLs may induce tumor cells to produce “malignancy factors”. Such factors may support the further expansion of tumors, for example by stimulating cells of the tumor microenvironment, by mobilizing novel (hematopoietic) cells involved in tumor growth, and/or by supporting pre-metastatic niches.

## GRANTS

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### GRANT "CANCER AND IMMUNOLOGY"

#### **Endoplasmic reticulum stress in cancer**

This "ISREC grant" amounting to CHF 40'000.- per year was awarded to Bojan Bujisic in January 2012 for four years.

**Bojan Bujisic** is working in the group of Prof. Fabio Martinon (Department of Biochemistry, UNIL).

#### **Introduction**

The endoplasmic reticulum (ER) is an essential organelle that detects perturbation of cellular functions and restores homeostasis via the induction of the unfolded protein response (UPR). Hypoxia, nutrient deprivation and pH changes that are commonly present within the tumor mass activate a range of cellular stress response pathways including the UPR. This response can trigger both pro-survival and pro-apoptotic signals. It is therefore essential to understand how modulation of the UPR alters the balance between these processes and contributes to carcinogenesis in different cell types. It has recently been shown in two independent studies that downregulation of XBP1, a UPR signaling protein, renders multiple myeloma cells less sensitive to Bortezomib (1, 2). In addition, overexpression of XBP1 was sufficient to promote the onset of multiple myeloma-like syndrome in mice (3). All together, these observations suggest a dual role of XBP1 in progression and treatment response of B cell malignancies.

Therefore, the identification and use of drugs that would direct the UPR in cancer cells towards promotion of cell death could lead to the development of new therapeutic strategies. Lately, it has been suggested that HIV protease inhibitors, a family of drugs used to decrease viral replication in HIV patients, exert an antitumor action by modulating a specific UPR response in multiple myeloma cell lines (4).

My project is aimed at elucidating the significance of the UPR signaling pathways in tumors by focusing first on the role of the IRE1-XBP1 signaling branch in diffuse large B cell lymphoma (DLBCL). In the first year report, I showed that the ER-stress sensor IRE1 is downregulated in germinal center B cell (GCB) lymphoma when compared to activated B cell-like (ABC) lymphoma; these are two specific subsets of DLBCL. Consequently the production of XBP1, a potent downstream transcription factor, was impaired in GCB cell lines after treatment with ER stress-inducing drugs.

#### **Results obtained in the 2<sup>nd</sup> year**

In contrast to the dramatic difference in IRE1-XBP1 expression, the PERK-ATF4 branch appeared to be equally functional in both ABC and GCB DLBCL subtypes. Treatment of various ABC and GCB cell lines with ER stress-inducing drugs (Tunicamycin, Thapsigargin) or the HIV-protease inhibitor Nelfinavir led to a similar induction of the ATF4 transcription factor in all tested conditions. In addition, in accordance with ATF4 activation, there was no variation in protein levels PERK, an upstream kinase.

These data indicated that GCB cells do not bear a general defect in the ER signaling platform but rather a specific downregulation of the IRE1-XBP1 signaling branch. These observations prompted us to reconstitute GCB cell lines with inducible vectors expressing IRE1 or XBP1, in order to define the role of this branch in the investigated B cell malignancy. Our results indicate that XBP1 reconstitution provides GCB cells with the capacity to mount a normal ER stress response characterized by an upregulation of the UPR-dependent genes, such as DNAJB9, upon treatment with ER stress inducers. These preliminary data indicate that IRE1 deficiency is a hallmark of GCB DLBCL tumors and could contribute to increased sensitivity to ER stress-inducing drugs, possibly providing us with new prognostic tools and therapeutic strategies in DLBCL patients.

## ...> ACADEMIC TRAINING

### Future directions

To address the physiological relevance of these findings, we designed two main strategies: First we will identify the role of XBP1 and IRE1 in the development and aggressiveness of DLBCL by modulating the expression of the pathway components and analyzing the outcome in vitro and in mice. To test this, we expressed IRE1 and XBP1 in GCB using an inducible lentiviral transduction system. Using this strategy we were able to reconstitute the pathways in 3 different GCB tumoral cell lines. We will monitor viability, proliferation and gene expression in GCB cells with a functional IRE1-XBP1 pathway.

Secondly, we will investigate whether deregulation of the UPR by therapeutics targeting the ER stress pathways, such as Nelfinavir and Bortezomib, could be exploited for the treatment of different DLBCL tumors, in particular, in tumors that display a defect in the XBP1-dependent adaptation response (GCB). This could lead us to the development of new diagnostic tools as well as new therapeutic strategies to target this type of tumors.

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## GRANTS

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### GRANT “MOLECULAR LIFE SCIENCES”

#### **Spatiotemporal control of proprotein convertases at cellular and tissue levels**

This “ISREC grant” amounting to CHF 80'000.- per year was awarded to Pierpaolo Ginefra in January 2013 for four years.

**Pierpaolo Ginefra** is working in the group of Prof. Daniel Constam (EPFL/SV/ISREC).

#### **Introduction**

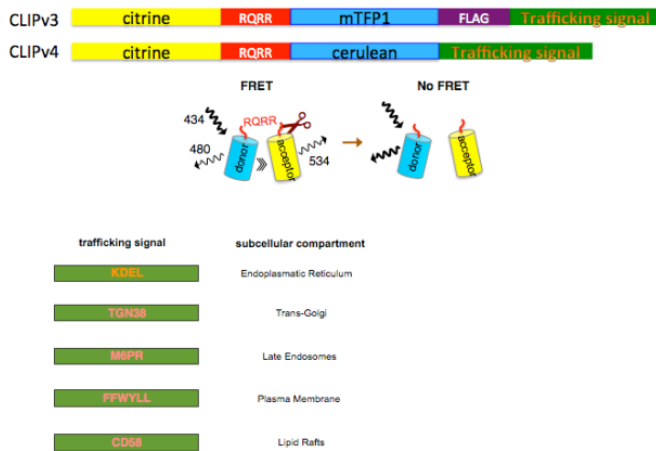
Secreted enzymes of the subtilisin/kexin type proprotein convertase (PCSK) family activate or inhibit various hormones, growth factors and cell adhesion molecules by mediating endoproteolytic cleavage of their precursors after recognition of specific motifs. However, their physiological roles in most tissues and in various diseases such as cancer have remained poorly defined, in part because of technical hurdles to clearly distinguish functionally overlapping PCSK activities by conventional experimental approaches. Many of the most common and deadly human cancers (e.g. lung cancers and melanoma) produce elevated levels of usually more than one PCSK. Alterations in their abundance and in the activities of critical substrates such as TGF $\beta$  or Notch generally correlate with tumor progression, invasiveness and metastatic growth. However, in order to interfere with these capabilities of cancers, a major question that needs to be answered is when and where in a given tissue and in specific subcellular compartments each of the nine PCSK family members is activated and thus capable of engaging specific subsets of potential substrates. Addressing these questions will be crucial to develop therapeutic tools to preferentially target pathogenic PCSK functions and to reduce the toxicity of systemic PCSK inhibitors.

#### **Results**

In this first year, I used two biosensors, CLIPv3 and CLIPv4, previously developed in the lab, to quantify PCSK activities in specific subcellular compartments in normal and cancer cells. The biosensors consist of two fluorophores linked by a sequence that is specifically cleaved by all of the most widely distributed PCSK family members. To target these probes to specific subcellular compartments, we fused them to a series of specific localization signals (Figure 1). The two fluorophores were chosen for their capability to perform Förster resonance energy transfer (FRET). Measuring FRET informs us on how much of the biosensor has been cleaved. High FRET values correspond to the uncleaved state while low FRET values indicate that the cleavage has occurred. Until now, PCSKs have been thought to cleave the majority of their substrates in the trans-Golgi network.

By contrast, our analysis of compartment-specific CLIPv3 and CLIPv4 variants in cultured cells suggests that PCSK activities are much higher in post-Golgi compartments. To quantify PCSK activities at the subcellular level, both in normal and cancerous cells, I measured FRET efficiency of our biosensor variants in cultured cells. I measured FRET efficiency for the uncleavable control biosensors mCLIPv3 and mCLIPv4 in order to quantify the maximum value, needed to normalize results obtained with CLIPv3 and CLIPv4 targeted in the lipid rafts and late endosomes. I found that while mCLIPv3 displayed no FRET activity at all, mCLIPv4 showed FRET activity, with efficiencies of 23% in lipid rafts and 30% in late endosomes (Figure 2). In order to elucidate where the cleavage of biosensors occurs, I combined the analysis of CLIPv3 and CLIPv4 processing in cells treated or not with various PCSK inhibitors. This study shows that our biosensors are suitable for analysis of PCSK activities using FRET. These biosensors will be further developed to improve the sensitivity of the FRET analysis, enabling us to draw a map of PCSK activities in normal and cancer cells.

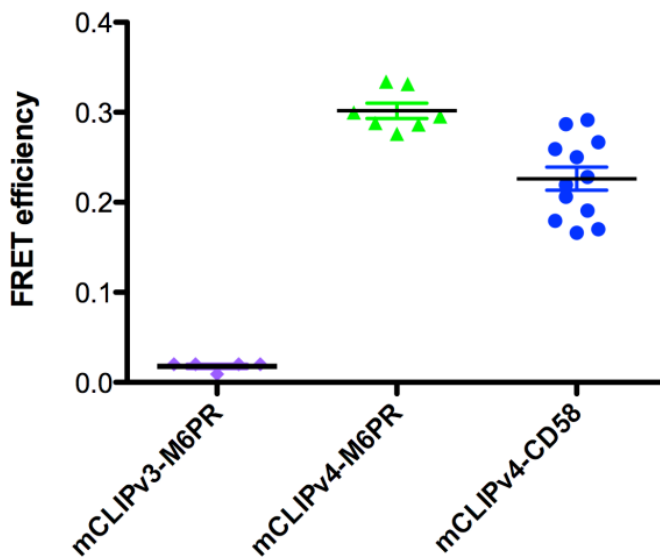
## ...> ACADEMIC TRAINING



**Figure 1**  
**Design of cell-linked indicator of proteolysis (CLIPV) biosensor variants**

Cleavage of the linker RQRR between the donor and the acceptor inhibits FRET. Table indicating the trafficking signals used to target the biosensor to the subcellular compartment of interest. KDEL sequence for the endoplasmic reticulum, TGN38 (TM domain and cytosolic tail of the human TGN38 protein) sequence for the TGN network, M6PR (TM domain and cytosolic tail of bovine cation-dependent mannose 6-phosphate receptor) sequence for late endosomes, FFWYLL (mutant TM domain and cytosolic tail of bovine cation-dependent mannose 6-phosphate receptor) sequence for the plasma membrane and CD58 (GPI anchor of the human CD58 protein) sequence for lipid raft domains.

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**Figure 2**  
**FRET efficiency analysis of mCLIP series in HEK293T cells measured by acceptor photobleaching**

FRET efficiency of the cleavage mutant control CLIP is obtained using the formula  $\text{FRET efficiency} = 1 - \text{ID}_{\text{pre}}/\text{ID}_{\text{post}}$  where  $\text{ID}_{\text{pre}}$  is the fluorescence intensity of the donor before the bleaching and  $\text{ID}_{\text{post}}$  is the fluorescence intensity of the donor after the bleaching.

## GRANTS

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### GRANT “MOLECULAR LIFE SCIENCES”

#### **Role of epithelial-to-mesenchymal transition in non-small cell lung cancer**

This “ISREC grant” amounting to CHF 80'000.- per year was awarded to Svenja Groeneveld in August 2013 for four years.

**Svenja Groeneveld** is working in the group of Prof. Etienne Meylan (EPFL/SV/ISREC).

#### **Introduction**

Lung cancer is the leading cause of cancer-related deaths worldwide. The most common form is non-small cell lung cancer (NSCLC). One of the genetic mutations, occurring in 15-25% of NSCLC cases, is an activation of the *K-ras* oncogene. The presence of this mutation is associated with a negative prognosis for overall survival and benefit from both targeted treatment and chemotherapy (Riely et al., 2009). Due to a largely asymptomatic onset, most NSCLC patients are diagnosed at an advanced stage when they already present metastatic disease (Saintigny, 2012). The main metastatic sites of NSCLC are the adrenal glands, bone, brain and liver (Quint et al., 1996).

In the last few years, a process called epithelial-to-mesenchymal transition (EMT) has been discovered to be associated with cancer progression, specifically with the formation of metastases. EMT plays an important role in normal physiology, specifically in the embryonic development and in the response to injuries. Epithelial cells line the cavities and (inner) surface structures of the human body, including the lung. Upon oncogenic transformation, they can give rise to carcinomas. During EMT, these cancer cells acquire mesenchymal features such as high motility and adhesion-free survival, which enables them to detach from the primary tumor and to disseminate through the blood stream. Upon seeding to distant sites in the body, the tumor cells undergo the reverse process, mesenchymal-to-epithelial transition (MET), to grow into life-threatening metastases (Thiery et al., 2009).

In different cancers, such as breast, cervical and colorectal cancer, EMT is associated with a poor prognosis (Thiery et al., 2009). Three main groups of transcription factors, namely the Zeb, Snail and Twist families, can induce EMT in epithelial cells (Sánchez-Tilló et al., 2012). Recently, one of these transcription factors, Twist1, was shown to contribute to the formation of lung cancer (Tran et al., 2012). In other cell types, however, different members of these families were found to have differential and even opposing roles. For example, some of them seem to have tumor-suppressing functions (Caramel et al., 2013).

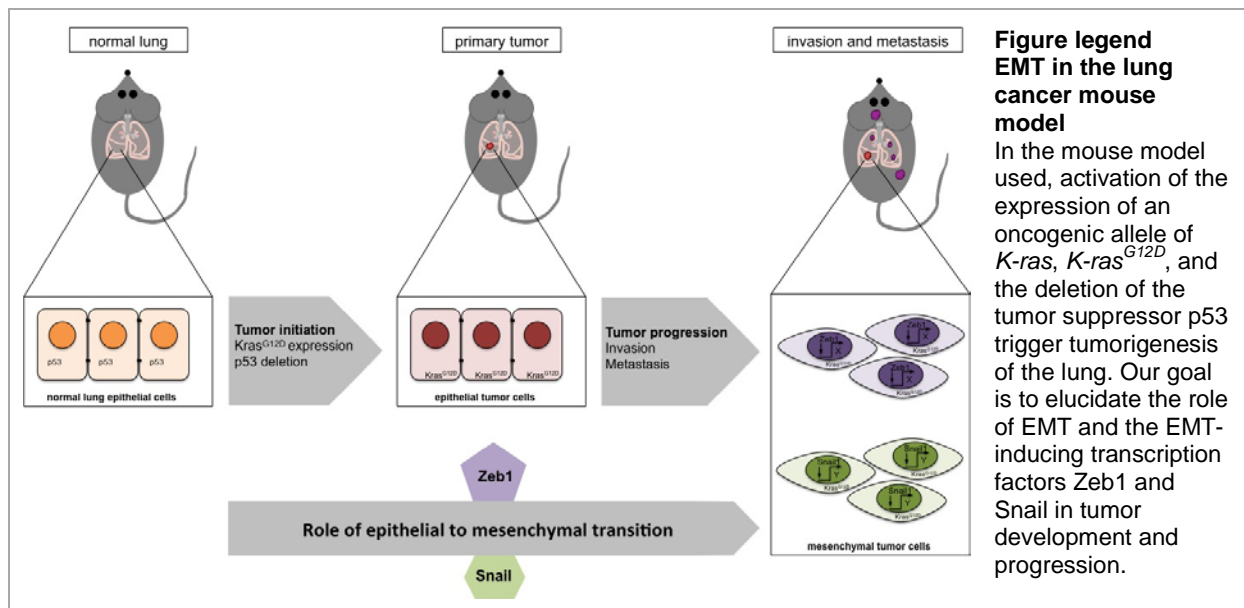
#### **Aims of the project**

My project involves the investigation of EMT in NSCLC. I am interested in the effects of EMT on invasion and in assessing whether it influences the onset and frequency of metastases formation. Furthermore, my goal is to dissect the contribution of the individual transcription factors to the phenotype. Specifically, the role of the members of the Zeb and Snail families has not yet been evaluated in lung cancer. Recently, we found that EMT causes the deregulation of a metabolic transporter, the high-affinity glucose transporter Glut3, in NSCLC. Therefore, I will assess whether EMT has similar effects on other metabolic transporters.

To model the human disease, our group employs a mouse model of lung cancer in which we activate an oncogenic allele of *K-ras* in the respiratory system. In addition, we can delete the tumor suppressor p53, resembling a mutational event that occurs in 50% of human lung cancers as well (Jackson et al., 2005). I would like to advance this mouse model by inducing or blocking EMT following modulation in the expression of the EMT-inducing transcription factors Zeb1 and Snail at different stages of lung tumorigenesis. With this advanced model, we aim to gain a better understanding of the human disease and to identify potential targets for improved therapies.



## ...> ACADEMIC TRAINING



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## CHAIRS

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### ISREC chairs

To reinforce its support and to promote the advance of translational oncology, the Foundation decided to create three “ISREC chairs”. These are created to give the possibility to young professors to start a career in research. Each chair is endowed with CHF 500'000.- per year for a period of six years and is financed by the fortune of the Foundation.

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### ISREC CHAIR “TRANSLATIONAL ONCOLOGY”

#### **Signaling mechanisms and novel treatment strategies for hematological malignancies**

This chair endowed with CHF 500'000.- per year for a period of six years was allocated in March 2011.

It was awarded to the research group of **Prof. Oliver Hantschel** (EPFL/SV/ISREC).

#### **Preamble**

The Hantschel laboratory started its operation 2.5 years ago at ISREC and is located on the main campus of EPFL. With the visionary and generous financial support of the ISREC Foundation and the excellent infrastructure provided by the School of Life Sciences at EPFL, I was able to assemble an international and interdisciplinary team of young, motivated and talented PhD students, postdoctoral fellows and technicians that work at the interface of protein biochemistry, medicine and cancer biology.

#### **Introduction**

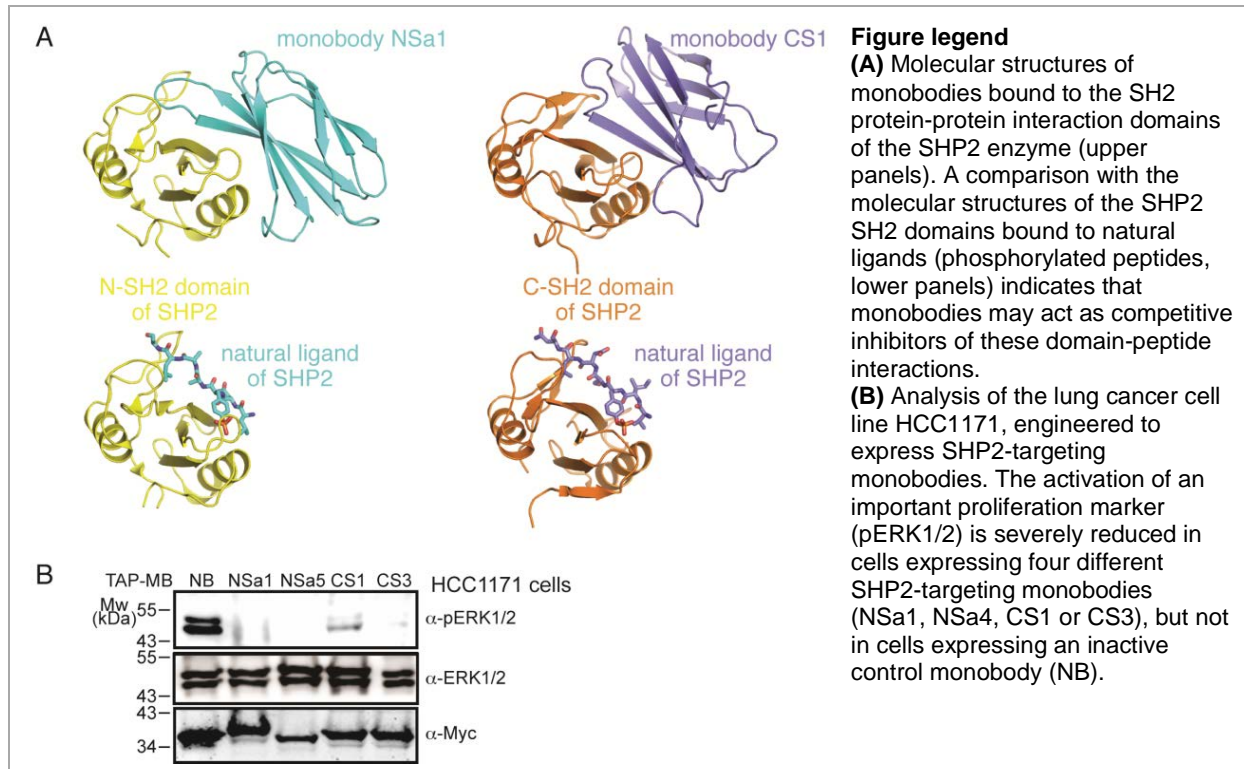
Our laboratory is interested in understanding the molecular changes that occur in cancer and in identifying novel and more effective possibilities to treat cancer specifically. We are primarily focusing on leukemias, which are cancers that are characterized by the overproduction of certain types of white blood cells in the bone marrow and their premature release into the peripheral blood. Most leukemias are fatal if not treated rapidly after diagnosis. Several aberrant changes in the genetic material of leukemia cells have been identified over the past 20 years and linked to the pathophysiology of this cancer type. Some of these changes can be treated using specific drugs, but most of them are still very difficult to target.

#### **Results**

In 2013, we published a widely-recognized study in 'Proceedings of the National Academy of Sciences USA', in which we engineered proteins, termed monobodies, that are tailored to bind very specifically to the phosphatase enzyme SHP2. SHP2 is critical for the transmission of oncogenic signals in different leukemias, but is also deregulated in other diseases, such as breast and lung cancer. No specific inhibitors existed previously. Work carried out by PhD student Emel Basak Gencer Akcok and lab manager Sandrine Georgeon in collaboration with investigators from Prof. Shohei Koide's laboratory at the University of Chicago now showed that monobodies selectively and potently inhibited SHP2 function and signal transduction pathways that are critical for growth and proliferation of leukemia and lung cancer cells. Our results delineated the molecular pathways that regulate SHP2 enzymatic activity and validated monobodies as potent and specific antagonists of protein-protein interactions in cancer cells. Ongoing and future projects in the laboratory intend to evaluate the utility of monobodies targeting other protein components that are important for cancer cell survival and the application of monobodies in combination with already used anti-cancer drugs.

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## ...> TRANSLATIONAL RESEARCH



A second major focus of our research, supported by a grant from the Swiss Cancer League, aims at targeting tyrosine kinases in unconventional ways. Tyrosine kinases are often aberrantly active in cancer. This class of enzymes adds phosphate groups to other proteins and thereby perpetuates the oncogenic signal. More than a dozen new drugs that specifically block these enzymes and show very good responses in cancer patients have entered the market in the past years. The main drawback of these drugs is that the targeted enzyme may adapt its structure and thereby become insensitive to the drug, so that the tumors start to grow again. Our aim is to identify alternative approaches to inhibit these enzymes. One way is to identify regulatory binding sites that are distinct from the site where the available drugs bind, with the hope to thereby delay the development of resistance.

### ISREC CHAIR "TRANSLATIONAL ONCOLOGY"

#### Molecular cancer immunotherapy and immune engineering

This chair endowed with CHF 500'000.- per year for a period of six years was allocated in June 2013.

It was awarded to the research group of [Prof. George Coukos](#) (UNIL/CHUV).

Assistant tenure track professor to be nominated.

## FUNDS

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### FUND “TRANSLATIONAL RESEARCH - STEM CELLS”

#### Discovery of new therapeutic targets in the tumor microenvironment

This “allocated fund” from a private donator and amounting to CHF 3.5 million was allocated in 2005.

It was awarded to the research groups of [Prof. Michel Aguet](#) (EPFL/SV/ISREC) and [Prof. Ivan Stamenkovic](#) (UNIL/CHUV).

#### Introduction

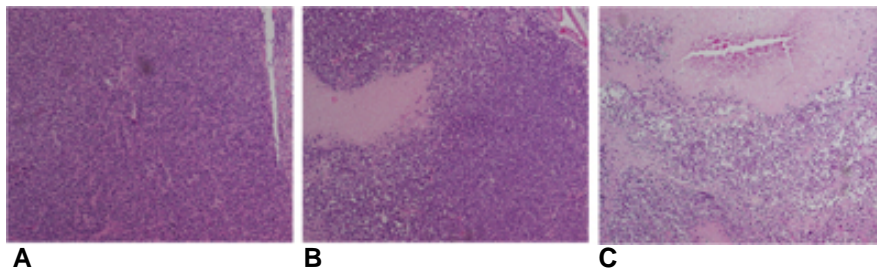
The vast majority of current anti-cancer therapies are geared toward eliminating highly proliferating cells, typically by blocking DNA synthesis during replication or by inhibiting cell division itself. It seems clear that such a strategy is hardly selective for tumors and that it is likely to cause severe toxicity to normal cells, which is indeed the case for practically all forms of chemotherapy. On top of that, classical anti-cancer chemotherapy has only transient efficacy in the majority of solid malignancies, with almost invariable relapse and progression as tumor cells become resistant to its effects. Therapy based uniquely on inhibition of cell division is not only weakly selective, if at all, but largely ignores the defining properties of malignant tumors, which are the capacity to invade adjacent tissues and to disseminate throughout the organism. Despite the development, in recent years, of a large number of more targeted drugs that are selective and less toxic, the necessity to address pathogenic mechanisms that underlie tumor dissemination and resistance to therapy remains. At the outset, our project was aiming to explore the influence of the tumor microenvironment on these properties. It is well established that the interface between the tumor and its surrounding stroma, where tissue remodeling akin to that observed in inflammation and wound healing occurs, is critical to tumor progression. In recent years, it has become clear that tumor-driven tissue remodeling is implicated in maintaining a subpopulation of tumor cells that harbor stem cell properties and whose role in tumor relapse following therapy and development of metastases is beyond doubt. Elucidation of the properties of these cells, referred to as cancer stem cells (CSC), has become an area of intense investigation with the hope of uncovering new therapeutic targets that may impact core properties of malignant cells with a major prognostic benefit.

Our two projects gradually focused on the validation of novel therapeutic strategies directed toward targeting CSCs. Thanks to the support of the Foundation, we were able to engage in a truly translational research avenue that has led to advanced pre-clinical studies and in one case to clinical application.

**Final report - The Stamenkovic group** pursued elucidation of mechanisms that lead to CSC emergence in a variety of malignancies and particularly in Ewing's sarcoma family tumors (ESFT). One lead came from our earlier observations that microRNAs (miRNAs), and notably miRNA-145, are repressed in ESFT CSC, and that their overexpression results in the loss of CSC properties. To address the functional role of miRNAs in CSC development, we assessed miRNA expression profiles in CSC and non-CSC ESFT cell populations. CSCs were observed to display suppression of a broad range of miRNAs compared to non-CSCs. Because each miRNA can regulate the expression of numerous genes, the observed downregulation of a broad panel of miRNAs could potentially have a highly significant impact on the gene expression profile of CSCs and govern their biological properties. CSCs give rise to more differentiated progeny that have lost CSC features, suggesting that the mechanism which suppresses miRNAs involved in CSC maintenance must be reversible. In searching for such a putative mechanism, we identified partial suppression of the gene that encodes TARBP2, a protein implicated in miRNA maturation in CSCs but not in non-CSC ESFT populations.

## ...> TRANSLATIONAL RESEARCH

TARBP2 was indeed found to be responsible for the maturation of a wide range of miRNAs in CSCs and its partial suppression explained the downregulation of their mature forms. Restoration of TARBP2 in ESFT CSCs abolished their self-renewal and tumor-initiating properties, suggesting that therapeutic TARBP2 targeting could be a valuable option for eliminating CSCs. A recent study showed that RNA interference could be augmented by enoxacin, an antibiotic that enhances TARBP2 activity. We therefore assessed the potential applicability of enoxacin to ESFT treatment. Our initial results indicated that enoxacin depletes CSC subpopulations in ESFT *in vitro* and *in vivo*, offering an unexpected and potentially attractive therapeutic reagent for ESFT. We subsequently addressed the effect of enoxacin in combination with conventional therapies aimed at eliminating the tumor bulk. Our results are highly encouraging, as they indicate that the combination of classical 'standard of care' chemotherapy and enoxacin causes massive tumor cell death. This results in dramatically reduced tumor size and elimination of CSCs, which are considered to be the driving force of the tumor. This combination has now been introduced into the clinic.



### Figure legend

Histology of Ewing sarcoma xenotransplants removed from mice treated with vehicle only (**A**), doxorubicin alone (**B**), and a combination of doxorubicin and enoxacin (**C**). Note the limited necrosis upon treatment with doxorubicin alone versus the massive necrosis in response to a combination of doxorubicin and enoxacin.

**Final report - Aguet group project:** Almost from the start, this project has focused on the Wnt pathway, known for its role in cell differentiation and in oncogenesis of the vast majority of colorectal cancers. The discovery by the group of Prof. Basler at the University of Zurich of a novel protein, BCL9, which is essential for this signaling pathway, has paved the way to a collaboration aimed at characterizing the role of this protein in mice. Our studies focused on mouse colorectal cancer models and revealed a critical role of this protein in CSC maintenance. Ablation of the protein did not prevent tumor formation, but tumors proved differentiated and by and large devoid of CSCs. Importantly, inactivation of BCL9 in established tumors rapidly induced differentiation and loss of CSC markers. These observations were confirmed in independent models, including human tumor cell lines, leading to a novel therapeutic concept, whereby standard chemotherapy aimed at reducing tumor mass would be combined with inhibition of BCL9 to reduce CSCs and thereby decrease the likelihood of tumor relapse. Despite the early stage of target validation and the novelty of this therapeutic concept, our group engaged in the search for small molecular compounds capable of inhibiting the interaction of BCL9 with its partner protein. In collaboration with the biomolecular screening facility at EPFL and partners in Germany and California, we screened libraries of 250,000 drug-like molecules and identified some hits capable of inhibiting the interaction specifically, but still requiring chemical optimization before they can be considered for further preclinical development. Next stages include *in vivo* experiments to establish proof of efficacy in mouse tumor models as well as first toxicity studies. The project will then have reached a stage at which further development will likely involve industrial partners.

## FUNDS

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### FUND “TRANSLATIONAL RESEARCH – GLIOBLASTOMA”

#### **Embryonic stem cells for the modelization of brain tumors**

This “allocated fund” from a private donator and amounting to CHF 350'000.-- was allocated to Dr. Olivier Preynat-Seauve in June 2011 for three years.

It was awarded to [Dr. Olivier Preynat-Seauve](#) (laboratory for immunohematology, University Hospital of Geneva).

#### **Introduction**

Glioblastoma is a brain tumor associated with a very severe prognosis. To understand the biology of these tumors and to discover novel therapeutic strategies, modelization in the laboratory is an important issue. Modelization consists in the ability to reproduce in vitro the in vivo situation in patients in order to study the disease. The best model currently available to study glioblastoma is the injection of human cancer cells into the mouse brain. This model is not optimal as it is based on a human/mouse interaction which does not represent the real in vivo situation in patients.

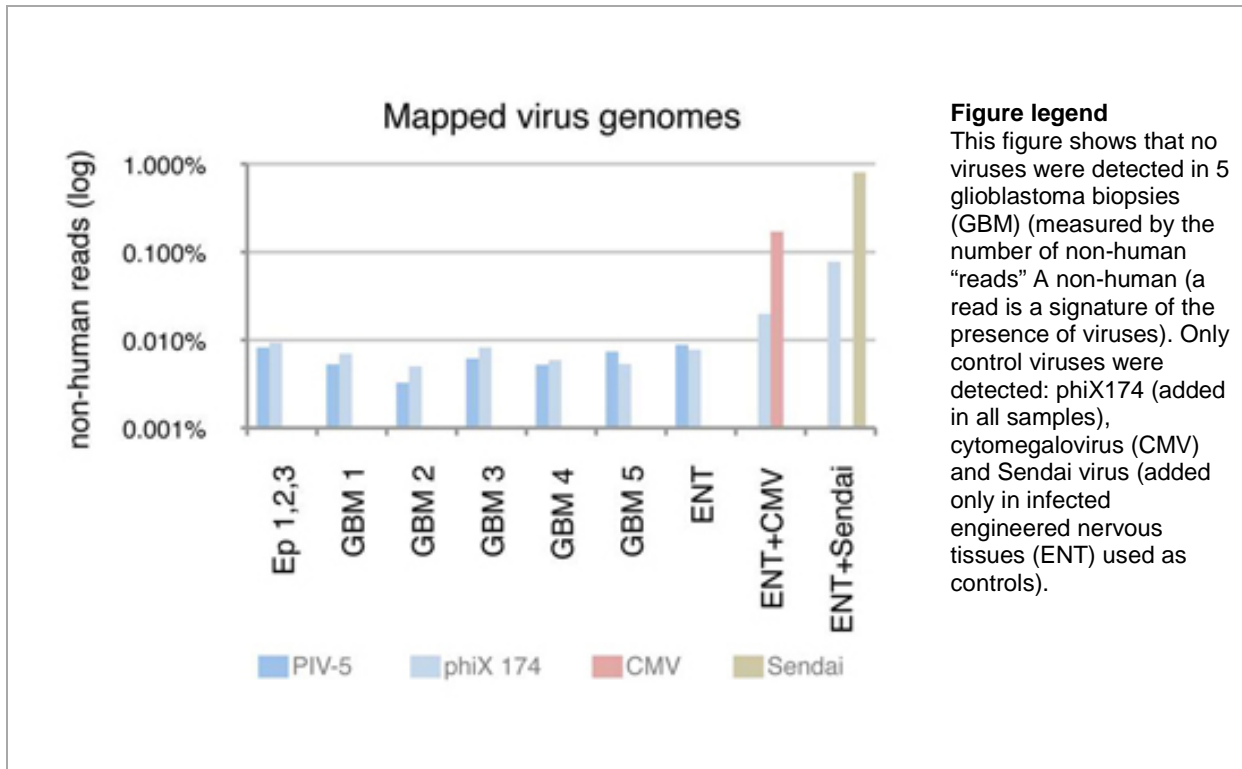
#### **Description of the project**

Using embryonic stem cells, we have developed a method to generate human brain-like tissue in vitro. Introduction of human glioblastoma cells into this tissue generates a tumor resembling the in vivo situation in patients, thus providing an innovative tool to study glioblastoma exclusively in the human species. The goal of our project is to develop this model and to use it for the understanding of the disease as well as to find new therapeutic compounds.

#### **Experiments done during 2013**

In 2012, the developed model allowed our team to identify a biological response called “type I interferon response”. This cellular response is generally associated with defense against viruses. Type I interferon response was also confirmed in vivo in five glioblastoma biopsies from patients, thus reinforcing the hypothesis that viruses might be present in the tumor and participate in disease aggressiveness. Moreover, there is currently a debate regarding the incidence of some viruses (e.g. cytomegalovirus) in glioblastoma. For this reason, we have decided to study the importance of viral activity in the disease in more detail. In a first step, in collaboration with the central laboratory of virology (Geneva University Hospital), current viral infection diagnosis methods were applied to biopsies. These experiments revealed the absence of viruses known to commonly infect the nervous system. To increase the sensitivity of the screen and in order to target all the currently known viruses, we therefore decided to develop a new tool based on emerging next generation nucleic acid sequencing methods. Nucleic acid sequencing makes it possible to detect, with a high degree of sensitivity, parts of the genome that are specific to a given virus. These are then used as molecular signatures of viral infection. We then developed and validated a new tool for complete virus screens in brain tumors, including sequencing and the bioinformatic pipeline required for data analysis. We were able to prove that active known viruses are absent in glioblastoma, thus providing new insights into the knowledge of the etiology of the disease.

## ...> TRANSLATIONAL RESEARCH



## FUNDS

### FUND “TRANSLATIONAL RESEARCH – CANCER IMMUNOTHERAPY”

#### Tumor targeting of innate and adaptive immune responses via combined CD1d-antitumor therapy and CpG-based cancer vaccine

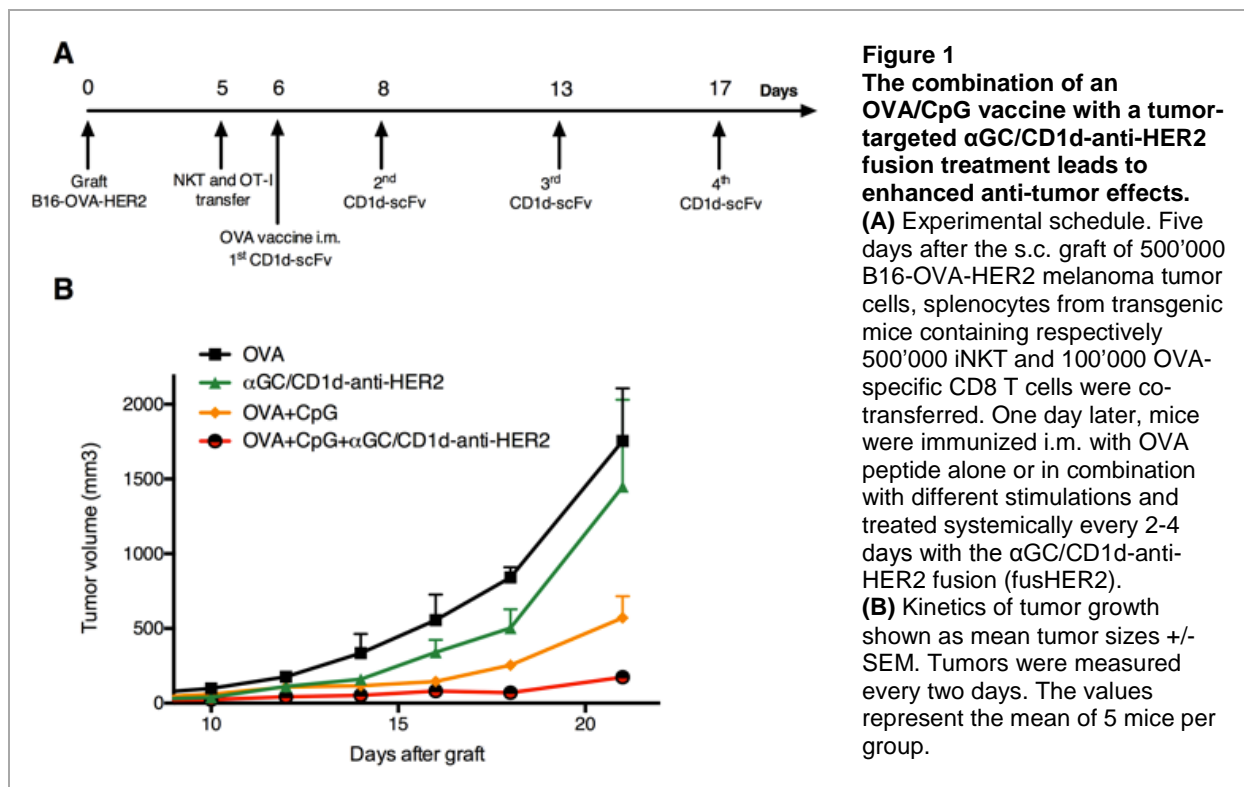
This “allocated fund” from a private donator and amounting to CHF 310'000.- was allocated in June 2011 for two years.

It was awarded to the research group of [Prof. Pedro Romero](#) (LICR@UNIL).

#### Final report

The present project aims to activate and redirect to the tumor site a particular population of T lymphocytes called iNKT cells, known to transactivate the innate and adaptive immune responses. The iNKT cells are activated by glycolipids (i.e.  $\alpha$ GC, alpha galactosyl ceramide) presented by the monomorphic MHC I-like molecule CD1d. This molecule is mainly expressed on antigen-presenting cells (APCs). Numerous pre-clinical studies as well as clinical trials have reported their anticancer activity. We have previously shown that sustained mouse iNKT cell responses can be induced by repeated stimulations with  $\alpha$ GC-loaded recombinant sCD1d-scFv fusion proteins. This leads to potent antitumor activity when CD1d is targeted to the tumor site by its fusion to an antitumor scFv antibody fragment. In previous reports, we have described the optimization of this strategy achieved by comparing different glycolipid analogs. In addition, we have convincingly shown in vitro the direct killing capacity of human iNKT cells when efficiently redirected against cancer cells by recombinant sCD1d-antitumor scFv fusion proteins targeting the relevant tumor antigen.

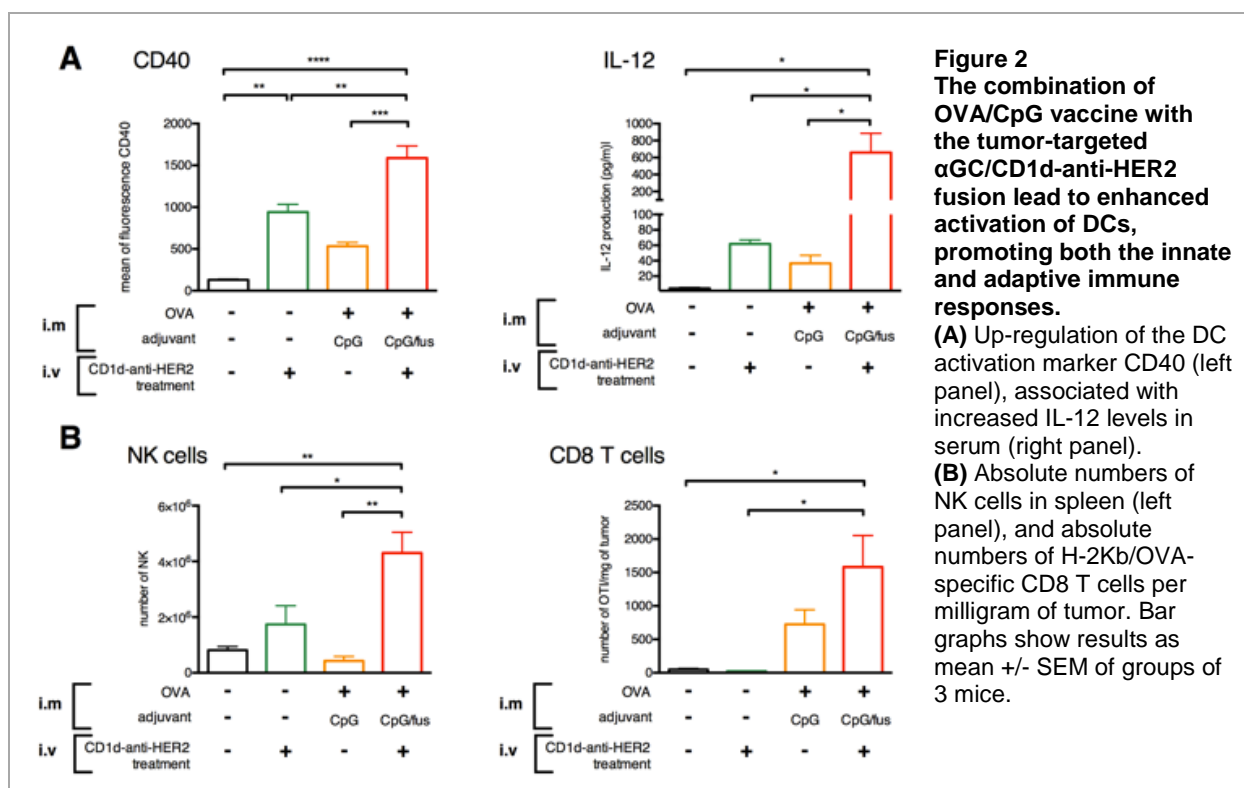
The research activity during 2013 aimed to combine iNKT-CD1d immunotherapy with therapeutic cancer vaccination, in order to exploit the capacity of iNKT cells to transactivate the adaptive immune response in addition to their intrinsic tumor cytotoxicity and natural killer (NK) cell transactivation. Indeed, we were able to demonstrate that antitumor effects could be greatly enhanced upon combined CD1d-anti-HER2 therapy and a tumor vaccine made of the peptide antigen OVA and the immuno-stimulating TLR-9 molecule CpG (Figure 1).





## ...> TRANSLATIONAL RESEARCH

We found that the expression of maturation markers was greatly increased on APCs such as dendritic cells (DCs) and monocytes, and associated with a peak of IL-12 secretion when CD1d-anti-HER2 therapy and OVA/CpG vaccine were combined (Figure 2A). The highly efficient maturation of APCs together with the sustained iNKT cell activation brought about by the CD1d-antitumor therapy resulted in optimized peripheral expansion of NK cells and H-2Kb/OVA-specific CD8 T cells (Figure 2B). Importantly, in mice primed with OVA/CpG and treated with tumor-targeted sCD1d-anti-HER2 fusion protein, the percentage and numbers of tumor-infiltrating H-2Kb/OVA-specific T cells was increased twofold compared to the 'vaccine alone' group (Figure 2B). The enhanced intratumoral CD8 T cell response correlated well with superior tumor growth inhibition of established B16-OVA-HER2 tumor grafts (Figure 1). Importantly, the anti-tumor effects of the OVA/CpG vaccine against B16-OVA-HER2 tumors were best ameliorated when combined to the tumor-specific  $\alpha$ GC/CD1d-anti-HER2 fusion, as opposed to the combination with the irrelevant  $\alpha$ GC/CD1d-anti-CEA fusion (data not shown). This observation further underlines the need to re-direct the overall immune response to the tumor site in order to develop an efficient cancer therapy. The possible mechanisms resulting in the iNKT- and the TLR-9 ligand-mediated synergistic antitumor effects are currently being investigated: i) we have recently shown that the CpG-based vaccine favors an increased ratio of effector T cells to T regulatory cells at the tumor site, which may be further enhanced by concomitant iNKT cell activation; ii) DC licensing by both activated iNKT cells and TLR-9 activation may promote efficient antigen cross-presentation and T cell memory formation; iii) the TLR-9 ligand may also have a direct co-stimulatory effect on iNKT cells.



### Conclusion

Altogether, our pre-clinical study in mice demonstrates that  $\alpha$ GC/CD1d-anti-tumor scFv fusion proteins greatly increase the efficacy of therapeutic cancer vaccines, firstly as an adjuvant during T cell priming, and secondly as a therapeutic agent to redirect immune responses to the tumor site.

## FUNDS

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FUND “TRANSLATIONAL RESEARCH – SARCOMA”

### **Immune infiltrates are prognostic factors in localized gastrointestinal stromal tumors**

Collaboration between the CHUV, Lausanne and the IGR, Paris

This “allocated fund” from a private donator and amounting to CHF 200'000.- per year was allocated in January 2012 for five years.

Unit INSERM U1015 and Center of Clinical Investigations IGR/Curie

Director: [Prof. Laurence Zitvogel](#) / IGR - Institute Gustave Roussy

#### **Introduction**

Cancer immunosurveillance relies on effector/memory tumor-infiltrating CD8<sup>+</sup>T cells with a Th1 profile. Evidence for an NK cell-based control of human malignancies is still largely missing. The gastrointestinal stromal tumor (GIST) is the most frequent mesenchymal tumor of the digestive tract (10-20 annual cases/million). 70-80% of GISTs harbor an oncogenic mutation in the type III receptor tyrosine kinase KIT, leading to ligand-independent receptor homodimerization and consequent kinase activation. The KIT tyrosine kinase inhibitor imatinib mesylate (IM) markedly prolongs the survival of patients with GIST by direct effects on tumor cells, as well as by indirect immunostimulatory effects on T and NK cells. Very few studies have addressed the immune infiltrate of GIST (1, 2).

#### **Results**

We have investigated the prognostic value of tumor-infiltrating lymphocytes expressing CD3, Foxp3 or NKp46 (NCR1) in a cohort of patients with localized GIST (4). Using systematic immunohistochemistry (IHC) and flow cytometric analyses, we have discovered that primary GISTs are infiltrated by activated NK cells and CD3<sup>+</sup> T cells. We have found that imatinib promotes the reduction of major histocompatibility complex (MHC) class I expression by tumor cells. CD3<sup>+</sup> tumor-infiltrating lymphocytes (TIL) were especially enriched in areas of the tumor that conserve class I MHC expression in spite of IM treatment (which theoretically may reflect a T cell-based immunoediting process). High densities of CD3<sup>+</sup> TIL predicted progression-free survival (PFS) in multivariate analyses (4).

Moreover, GISTs were infiltrated by a homogeneous subset of cytokine secreting -CD56<sup>bright</sup> (NCAM1) NK cells that accumulated in tumor foci after IM treatment. The density of NK cell infiltrates represents an independent prognostic factor that adds prognostic information to the Miettinen score for optimally resected primary GIST (4). In addition, T cells appear to play a major role in the immunosurveillance of GISTs harboring exon 11 mutations. The Foxp3 infiltrates (as measured in IHC) were positively correlated with the high-risk Miettinen score and to a lesser extent with the mutational status (exon 11 mutations of KIT). The Foxp3 infiltrates strongly decreased post-IM, as previously described (3).

Given that T and NK subsets did not colocalize within the same areas of the tumor, that they did not correlate with each other in terms of frequency and that they added prognostic values to different mutations, we postulate that they should be considered as cooperating, yet independent factors that both influence the clinical outcome of localized GISTs. Based on the results obtained in this limited series of patients, we anticipate that the accurate quantification of the density and function of distinct lymphocyte subsets will refine current methods of risk stratification in GISTs and hence possibly guide therapeutic decisions.

## ...> TRANSLATIONAL RESEARCH

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## FUNDS

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### FUND “TRANSLATIONAL RESEARCH – SARCOMA”

#### **Mechanisms of sarcoma initiation and development**

Collaboration between the CHUV, Lausanne and the IGR, Paris

This “allocated fund” from a private donator and amounting to CHF 300'000.- per year was allocated in January 2012 for five years.

Research laboratory: Institute of Pathology, UNIL/CHUV, Lausanne

Director: [Prof. Ivan Stamenkovic](#)

#### **Introduction**

Sarcomas are malignant tumors of bone and soft tissues that comprise about 2% of all human malignancies but as much as 15% of pediatric cancers. Despite multimodal therapy, most sarcomas retain poor prognosis with a high metastatic proclivity. Part of the reason for this is that sarcoma biology is still poorly understood.

#### **Aims of the project**

We have undertaken studies aimed at identifying the cell of origin of a variety of sarcomas with the goal of elucidating the oncogenic events that lead to primary cell transformation and subsequent development of full-fledged tumors with the ability to metastasize. We showed that bone marrow-derived mesenchymal stem cells (MSC) are cells of origin of Ewing's sarcoma, the second most common bone malignancy of children and young adults, and of myxoid liposarcoma. However, there is increasing evidence that other sarcomas, including osteosarcoma and synovial sarcoma also originate in MSC subsets.

Our observations led us to address mechanisms whereby MSC become transformed to develop different types of sarcoma. We found that the fusion gene, EWS-FLI1, that is characteristic of Ewing's sarcoma and arises as a result of a specific chromosomal translocation, induces a series of epigenetic modifications in MSC that lead to transformation. These modifications include changes in chromatin structure which alter the expression of key genes that regulate cell survival and proliferation as well as changes in expression of small non-coding RNAs, known as microRNAs (miRNAs) that control the expression of entire networks of genes. We were able to show that modulation of the miRNA expression profile in MSC leads to the emergence of cancer stem cells (CSC) in Ewing's sarcoma. Cancer stem cells are believed to constitute the driving force in most malignancies in that they have the ability to self-renew and to give rise to more differentiated cancer cell progeny that constitutes the tumor bulk. Because CSCs typically divide slowly, they are relatively unharmed by conventional anti-cancer therapies aimed at eliminating rapidly proliferating cells.

#### **Results after the second year**

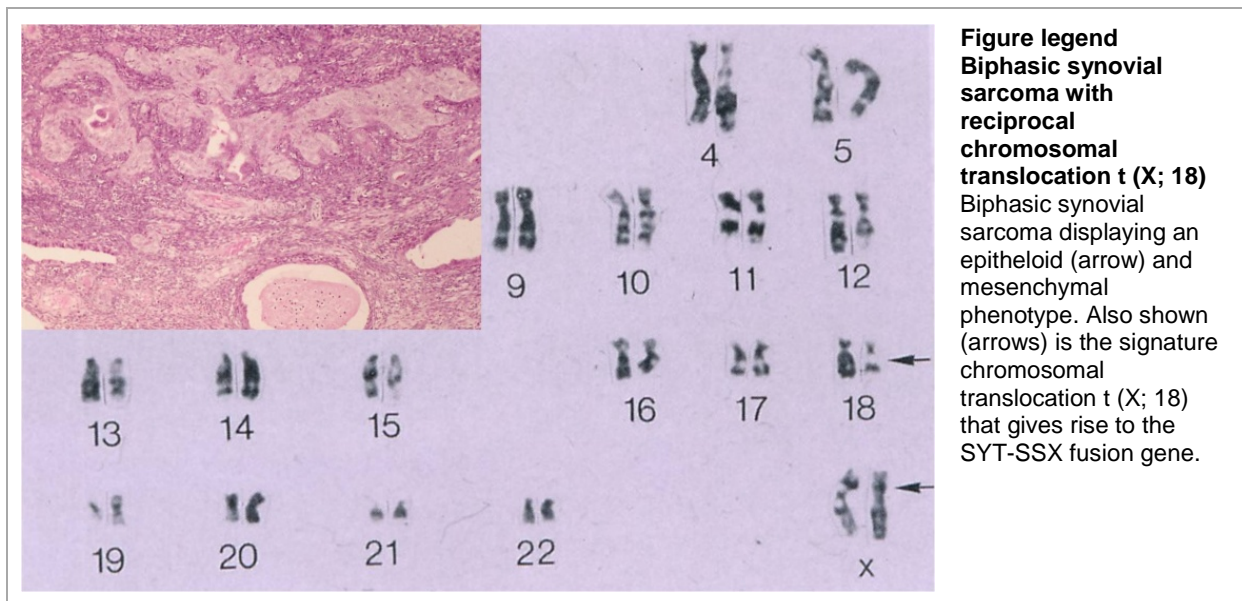
In 2013, we pursued three major avenues of sarcoma research. The first was the continuation of our work on Ewing sarcoma cancer stem cells (CSC) and, more specifically, the study of a combination of targeted therapy aimed at eliminating CSCs and conventional therapy aimed at the tumor bulk. In our earlier work, we showed that enoxacin can restore microRNA expression in CSCs and lead to their differentiation with loss of self-renewing and tumor initiating properties. Based on these findings, we assessed the effect of a combination of enoxacin and doxorubicin on primary Ewing sarcoma xenografts in immunocompromised mice. We observed that combining enoxacin and doxorubicin (which constitutes the standard of care cytotoxic drug in Ewing sarcoma) is far more effective in preventing tumor growth than either drug used alone. As enoxacin has long been approved for the treatment of infections, we plan to launch clinical trials of the combination of enoxacin and standard chemotherapy in Ewing sarcoma.

## ...> TRANSLATIONAL RESEARCH

Our other work on Ewing sarcoma focuses on mechanisms of metastasis and a comprehensive assessment of epigenetic changes that drive or maintain the CSC phenotype.

In parallel, we have been addressing the effect of expressing fusion genes associated with other sarcomas in human adult and pediatric mesenchymal stem cells (MSC). Several of these fusion genes have been successfully expressed in MSCs and we have begun a systematic analysis of the changes in gene and microRNA expression profiles in response to their expression. We have also initiated a systematic study of the effect of defined culture conditions (reprogramming or not) on the permissiveness of MSCs for the oncogenic effects of sarcoma fusion genes. This should allow us to determine the microenvironmental conditions that render MSC more or less permissive to transformation by sarcoma fusion genes and to unravel the corresponding epigenetic changes.

Finally, we are pursuing the study of the pathogenesis of synovial sarcoma, a highly aggressive malignancy occurring primarily in young adults and associated with a unique chromosomal translocation that generates the SYT-SSX fusion gene. The fusion protein encoded by SYT-SSX behaves like a transcriptional regulator but its mode of action is still obscure. We now have evidence that SYT-SSX selectively activates the Wnt signaling pathway which, in addition to regulating cell proliferation, plays a major role in determining cellular pluripotency and thereby participating in CSC maintenance. We are currently investigating the precise molecular mechanisms whereby SYT-SSX alters Wnt signaling in a way that ensures synovial sarcoma cell survival and tumor-initiating capacity.



## FUNDS

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### FUND “TRANSLATIONAL RESEARCH – CANCER IMMUNOTHERAPY” **Engineering T lymphocytes for long-term cancer therapy**

This “allocated fund” from a private donator and amounting to CHF 235'000.- was allocated in June 2013 for two years.

It was awarded to the research group of [Dr Nathalie Rufer](#) (LICR@UNIL).

#### **Project description**

CD8 T cell responses rely on the specific recognition by T cell receptors (TCRs) of small immunogenic peptides presented in the context of MHC class I molecules at the surface of infected or transformed cells. Binding of TCR to peptide-MHC (pMHC) is characterized by relatively weak molecular affinity. Although tumor-reactive T lymphocytes can be detected in cancer patients, these immune responses often fail to control or eliminate the disease. It has been proposed that T cells directed against tumor antigens express TCRs of lower affinity than pathogen-specific T lymphocytes.

Recent progress unveiling the cellular and molecular basis of the immune response allows nowadays the design of novel strategies for tumor immunotherapy. Adoptive transfer of T-cells engineered with TCRs has been recently developed with the aim to establish and boost immune reactivity towards poor immunogenic tumors. An attractive approach to improve this strategy is to optimize the TCR sequence with the aim to increase its affinity for cognate tumor antigen.

We recently optimized a human TCR gene sequence specific for the tumor antigen NY-ESO 1 and found that T cell function can be improved by increasing the TCR-pMHC affinity within physiological limits (1). Remarkably, our study showed that further increases led to drastic functional declines (2), revealing the presence of an affinity window for optimal T cell function (see Figure). We also described the presence of inhibitory regulators that “calibrate” T cell activation and function towards optimal responsiveness (3). In summary, we propose that the affinity of newly designed tumor-specific TCRs may not need to be optimized beyond the natural TCR affinity range to achieve optimal T cell functionality (see Figure). These findings emphasize the importance and feasibility of generating anti-tumor specific TCRs of optimal function but limited toxicity for use in clinical settings.

#### **Publications**

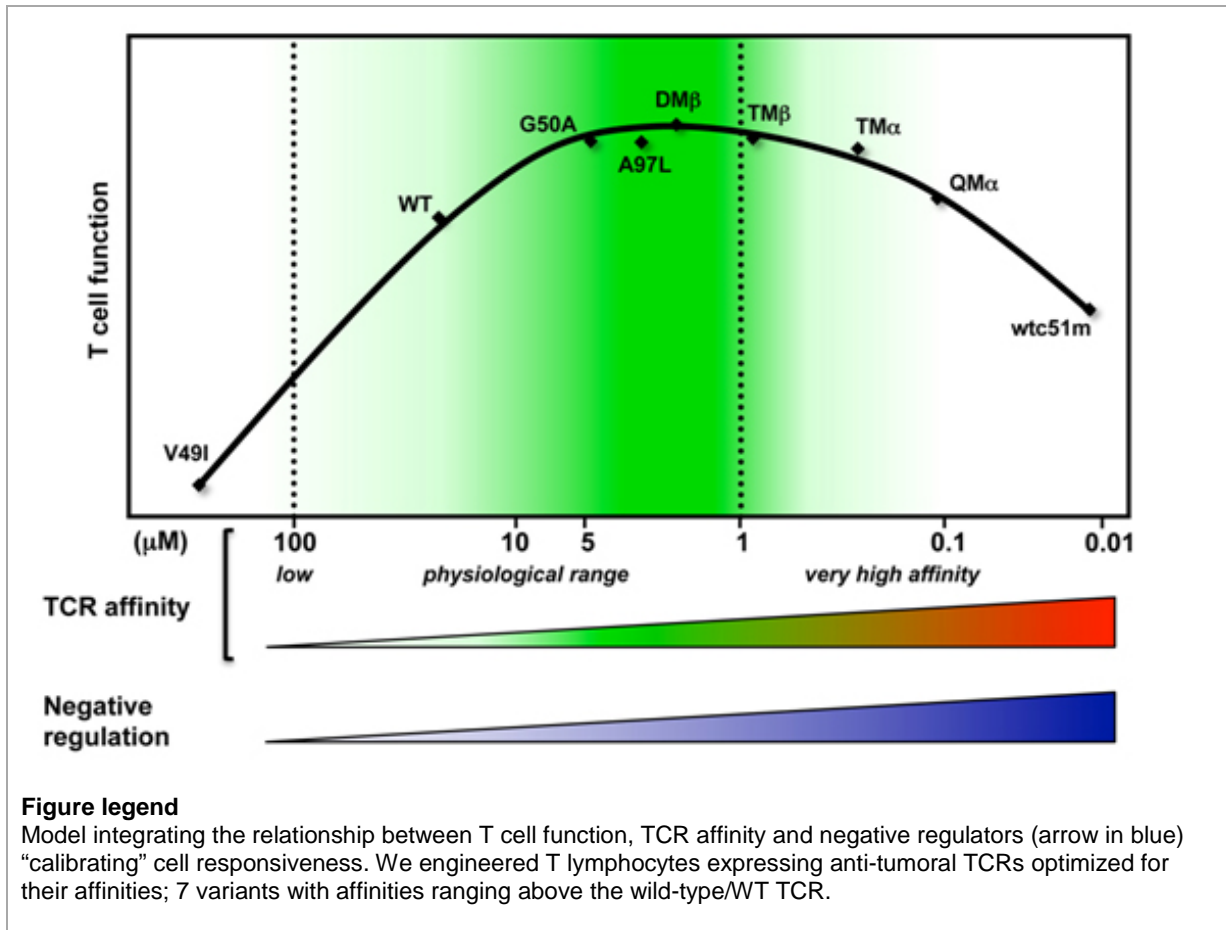
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#### **Specific aims**

At present, we need to find better ways to more effectively activate these T cells, to enhance their function and establish persistent long-term anti-cancer responses. Active immunization is most successful when using live-virus vaccines, essentially yellow fever virus 17D and smallpox vaccinia virus (Dryvax). Both have been shown to elicit in healthy donors multivalent immune responses, including strong primary CD4 and CD8 T cell responses. In this project, supported by the ISREC Foundation, we propose to generate and use cytolytic T lymphocytes specific for live-virus vaccines, and engineer them to co-express optimized tumor-specific TCRs. We hypothesize that activation of such dual T cells will provide optimal cell signaling through the vaccine virus-specific TCR, thus allowing efficient expansion, tumor cell killing and persistence over time. Precisely, we will characterize cell activation, signaling and functionality of CD8 T cells with dual specificities for virus vaccine and tumor antigens. We will further assess the impact of dual TCR cells on T cell expansion, persistence, and tolerance following serial vaccine boosts against the virus vaccine-specific TCR.

## ...> TRANSLATIONAL RESEARCH

These studies aim at understanding the impact of T lymphocytes with dual specificities for virus vaccine and tumor antigens in generating long-term memory responses and should provide rationales for the improvement of anti-cancer T cell based therapies.



## ORGANIZATION

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**Founded on June 18<sup>th</sup> 1964, the ISREC Foundation is a private non-profit foundation.**

The Foundation started its activity with the creation of the Swiss Institute for experimental cancer research. Today its mission is to select and support translational cancer research projects and so to help the transfer of knowledge and collaboration between fundamental research and clinical research. The goal of these innovative projects is to translate discoveries into results and to have a positive impact on the future treatment of human cancer.

**The Foundation is composed of:**

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## ORGANIZATION

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**Prof. Francis-Luc Perret**, Director

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The financial auditors, whose tasks are allotted by law, are nominated by the Foundation Council. They are elected for one year. The 2013 mandate was entrusted to **Ernst & Young**, Swiss Fiduciary and Audit Company recognized by the Swiss Institute of Certified Accountants and Tax Consultants.

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To enable the Foundation to work towards its goals, the following resources are available: legacies, gifts, donations, the product of its fortune and all other resources.

On December 31<sup>st</sup> 2013, the fortune of the foundation amounted to 47 million of francs.

### THE ISREC FOUNDATION IN 2013

<b>Total of subsidies remitted in 2013</b>	<b>CHF</b>	<b>2'227'458</b>
<b>in support of scientific and academic training</b>	<b>CHF</b>	<b>353'000</b>
Grant "Richard et Rita Barmé"		balance paid in 2012
Grant "Molecular biology of cancer and infection"		balance paid in 2012
Grant "Cancer and immunology"	CHF	40'000
Grant "Cancer and immunology"	CHF	40'000
Grant "Cancer and immunology"	CHF	40'000
Grant "Cancer and immunology"	CHF	40'000
Grant "Molecular Life Sciences"	CHF	80'000
Grant "Molecular Life Sciences"	CHF	80'000
11 Grants "International Summer Research Program"	CHF	33'000
<b>in support of translational cancer research</b>	<b>CHF</b>	<b>1'759'000</b>
ISREC Chair "Translational oncology"	CHF	524'000
ISREC Chair "Translational oncology"	CHF	500'000
Fund "Translational research - stem cells"		balance paid in 2012
Fund "Translational research - glioblastoma"		balance paid in 2012
Fund "Translational research - cancer immunotherapy"		balance paid in 2012
Fund "Translational research – sarcoma" - IGR	CHF	200'000
Fund "Translational research – sarcoma" - CHUV	CHF	300'000
Fund "Translational research – cancer immunotherapy"	CHF	235'000
<b>Project AGORA – Cancer Center</b>	<b>CHF</b>	<b>115'458</b>
<b>Total gifts, donations, legacies, external grants received in 2013</b>	<b>CHF</b>	<b>6'634'699</b>
66 spontaneous gifts from private individuals	CHF	182'644
25 gifts from companies, associations, foundations	CHF	443'000
2 gifts for allocated grants / funds	CHF	405'888
111 gifts in memory of deceased people	CHF	46'134
12 legacies, successions	CHF	5'557'033
<b>Capital of the Foundation (Free funds)</b>	<b>CHF</b>	<b>36'650'327</b>
<b>Reserved capital (Limited allocation funds)</b>	<b>CHF</b>	<b>8'292'450</b>
Grants	CHF	800'000
Funds	CHF	442'450
Fund "Echec au Cancer de la Broye" (equipment AGORA – Cancer Center)	CHF	50'000
ISREC chairs	CHF	7'000'000
<b>Reserved capital AGORA – Cancer Center</b>	<b>CHF</b>	<b>2'779'709</b>

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The financing of the ISREC Foundation projects is mostly assured by donations and legacies from people aware of, and keen to help, our cause. Your support is therefore essential to the pursuit of our mission: the support of cancer research projects and the training of young scientists in Switzerland.

**You can support our mission in various ways:**

- > by a donation
- > by the sponsoring of graduate students
- > by the sponsoring of young professors affiliated to a Swiss university or Institute
- > by the sponsoring of post-doctoral scientists for the development of projects of high competence at the national level
- > by a legacy

Whether modest or more important, every donation counts and contributes to our mission.

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The information available on the Zewo foundation web pages ([www.zewo.ch](http://www.zewo.ch)) is applicable.

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The ISREC Foundation is recognized as a non-profit institution of public utility. Therefore your donations are exonerated from communal, cantonal and federal taxes.

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**We are very grateful and thank each one of them most warmly.**

Among these donors, more than five hundred appear in our gold book:

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