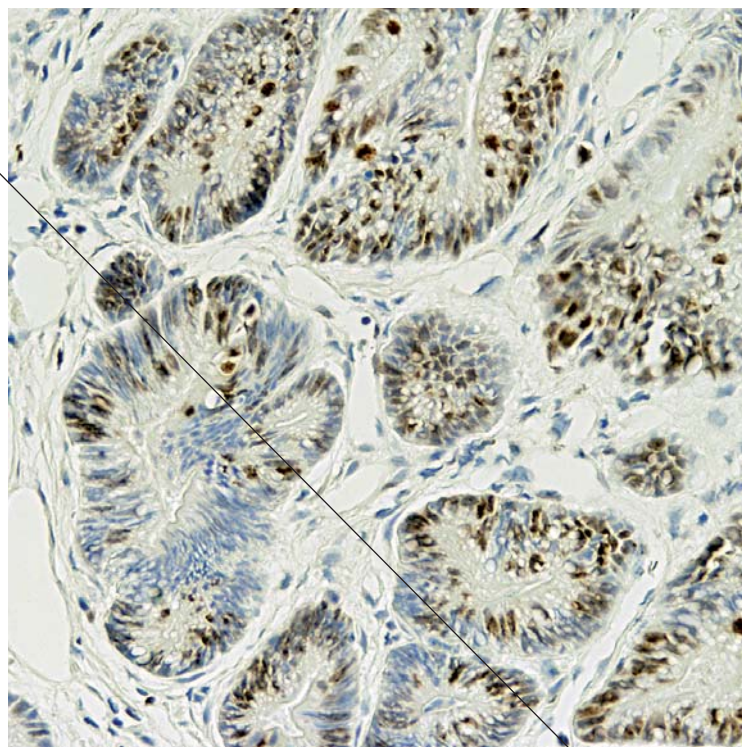


ANNUAL REPORT 2014

ISREC FOUNDATION

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



CONTENT

Editorial	1
Preface from the President of the Foundation Council	
Cancer research	2-3
Cancer facts and figures / Very encouraging results / Evolution of cancer death in Switzerland (1993-2012)	
Highlights 2014	4
Events organized in favor of the ISREC Foundation	
AGORA – Cancer center	5
Project	
Projects supported	6
Summer Research Program	
Grants	7-18
Cancer and Immunology / Molecular Life Sciences	
Chairs	19-22
Translational Oncology / Fundamental Oncology	
Funds	23-32
Glioblastoma / Sarcoma / Cancer Immunotherapy / Fundamental research	
Organization	33
Foundation Council / Scientific Board / Management / Financial auditors	
Finances	34
Support the ISREC Foundation	35
Make a donation / Fiscal deductions / Taxation	
Book of donors	36
Acknowledgements	

EDITORIAL

2014, JUBILEE YEAR AND FUTURE PERSPECTIVES

MESSAGE FROM THE PRESIDENT OF THE FOUNDATION COUNCIL

Dear donors, friends and partners,

Two important events have marked the year 2014 for the ISREC Foundation with, on the one hand, the celebration of fifty years of activity supporting cancer research projects and on the other, finalizing the official request to the authorities for the building permit for the Agora - Cancer Centre.

Since its creation on the 18th of June 1964, the Foundation has promoted research leading to significant discoveries, notably in the areas of mutagenesis, genome instability and repair, immunology, the cell cycle, cell biology, tumor virology, oncogenes, cell differentiation and bioinformatics. The work accomplished by the scientists and doctors supported by the Foundation has contributed over several decades to a better understanding of the mechanisms underlying cancer and to identifying new therapeutic targets.

Today, with the construction of the Agora - Cancer Centre building, the bringing together of the scientific and medical worlds marks a new phase that will, without doubt, open new perspectives for the scientists whom we support.

Faithful to our primary mission, the support of cancer research, we have awarded grants to students of the UNIL/EPFL summer program to enable them to undertake laboratory research. We have also endowed a new chair in translational oncology to support Prof. Elisa Oricchio who has been appointed Assistant Professor Tenure Track in the Faculty of Life Sciences of the EPFL (EPFL/SV/ISREC) in November 2014.

The many successes that have marked the history of cancer research and the statistics of the last few years show encouraging results. In this positive spirit our Foundation pursues its supportive role. It is this role that we are able to fulfil thanks to your engagement and your loyalty. Your participation is essential to the success of our projects.

A great thank you to you all,



Yves J. Paternot

CANCER RESEARCH

CANCER FACTS AND FIGURES

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

In Switzerland, about 38'000 new cases and 16'500 deaths are registered each year (National Institute for Cancer Epidemiology and Registration estimate for 2011 – NICER, 2014).

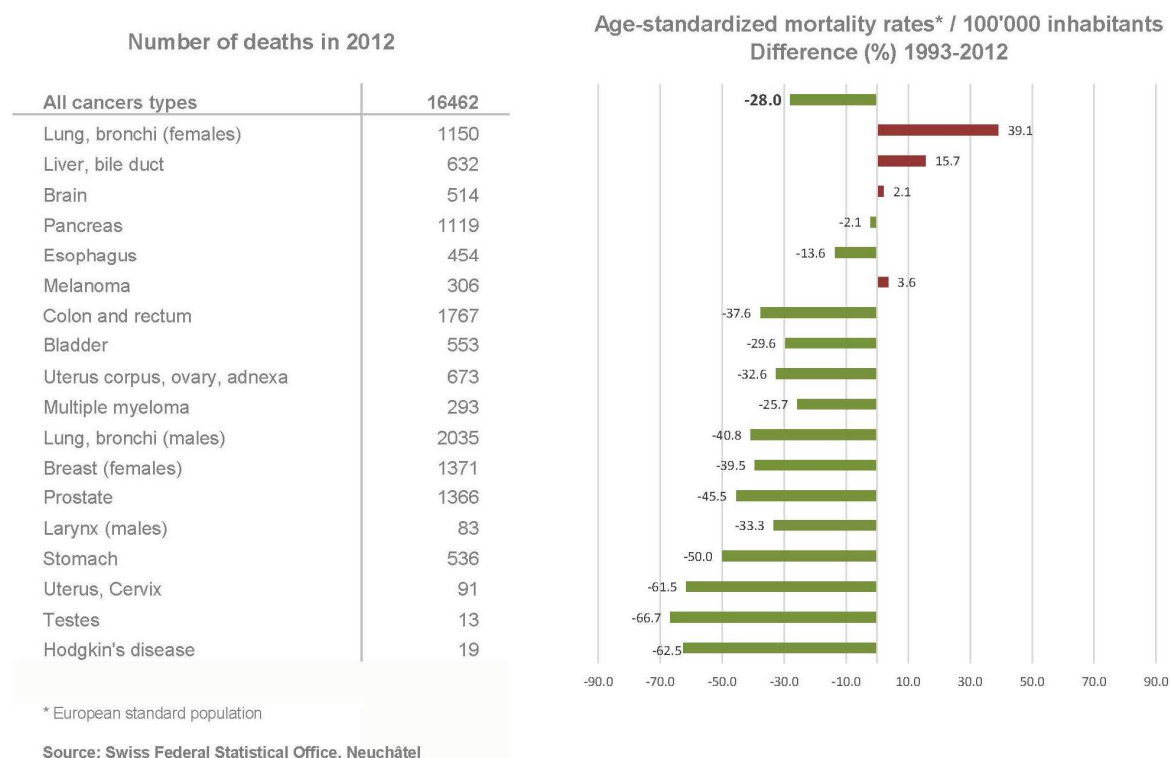
Approximately 127'000 people suffer from a cancer diagnosed less than 5 years ago (prevalence) (Source: Globocan 2012).

Today, in Switzerland, four out of ten people (one out of two men and one out of three women approximately) develop cancer during their lifetime and, unfortunately, the disease can be cured in only six out of ten cases.

The risk of developing cancer before the age of 70 is approximately 25% for men and 20% for women (Sources: FSO, NICER, 2012).

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

EVOLUTION OF CANCER DEATHS IN SWITZERLAND (1993-2012)



VERY ENCOURAGING RESULTS

Even though the number of cancer cases has increased over the last two decades (in particular because of the ageing of the population), there has been a noticeable decrease in overall death rates for cancer (-28% between 1993 and 2012), owing to improved diagnostic and therapeutic methods as well as to earlier cancer detection.

In women, the most frequent cancer (in terms of deaths in 2012) is breast cancer, followed by lung cancer and then by colon and rectum cancer. At diagnosis (incidence 2011): 1) breast, 2) colon and rectum, 3) lung and 4) melanoma (Sources: FSO, NICER, 2013).

In men, the most frequent cancer (in terms of deaths in 2012) is lung cancer, followed by prostate cancer and then by colon and rectum cancer. At diagnosis (incidence 2011): 1) prostate, 2) lung, 3) colon and rectum and 4) melanoma (Sources: FSO, NICER, 2014).

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

However, one must note that lung cancer mortality has notably increased among women, as a consequence of the rising number of smokers in young generations, whereas it has decreased in men.

Although cancer mortality is decreasing, the disease is unlikely to disappear completely. Therefore, the long term objective is rather to convert it into a chronic disease which can be controlled and/or cured.

Note that in 1990, there were approximately 140'000 people living in Switzerland who had been diagnosed with cancer ("cancer survivors"). Since then, this number has increased continuously. It is estimated that in 2015 there will be 316'500 cancer survivors in the country, amounting to approximately 4% of the Swiss population (Source: NICER). This rapid evolution generates an increased need for care and novel assistance models adapted to the reinsertion requirements of long-time survivors.

IMPORTANT EVENTS

EVENTS ORGANISED IN FAVOUR OF THE ISREC FOUNDATION

EXHIBITION IN CHAMPÉRY – PEOPLE

This unique event, supported by the Champéry tourist office, was organised on the initiative of Mr Richard Burton, an artist and painter who has survived cancer. Mr Burton has for this occasion edited a book of drawings representing the people of Champéry. The profits from the sale of the book have been donated to the Foundation, a total of CHF 2'761.15.

AGO TROPHY, LONAY

Fifty volunteers contributed to the success of the fourth edition of this trophy in memory of their friend Agostino who died of cancer. Close to 400 people were present and took part in the different activities and tournaments organised in Lonay on the 22nd of June 2014. The success of this event enabled the organisers to make a donation of CHF 9'000.-.

MOTORCYCLE HILL CLIMB “CORCELLES-LE-JORAT”

Since 1998 the Club Team Girard that includes owners, riders and fans of vintage motorcycles organises a hill climb event for Old-timers each year and donates half of the profits to the ISREC Foundation. Following the seventeenth edition, which took place on the 30th and 31st of August 2014 in Corcelles-le-Jorat, CHF 1'000.- have been generously donated.



AGORA – CANCER CENTER

THE ISREC FOUNDATION RESPONSIBLE FOR A MAJOR PROJECT

The Agora project has the goal of creating, on the Lausanne hospital site, an infrastructure of the highest quality able to welcome, from 2017 on, almost 300 scientists and clinicians.

Thanks to the Agora project, the ISREC Foundation, responsible for organising the construction of this building, supports the new interdisciplinary centre for applied cancer research which will bring together the competence of the universities, the federal institutes of technology (EPFs), hospitals, clinics and public and private institutions.



This building will bring together multi-disciplinary teams composed of doctors, biologists, immunologists, bioinformaticians and bioengineers from the different partner institutions. Their numerous and constant interactions will accelerate the development of new therapies and enable patients to benefit from them straight away.

The integrated and interactive AGORA centre will, in the near future, enable progress in our understanding of the mechanisms underlying each type of pathology and in developing targeted and optimised therapies for the benefit of patients.

Scientists and clinicians will together be able to provide answers to the multiple challenges posed by cancer, whether by the exchange and confrontation of points of view, of diagnoses or therapeutic approaches.



Interior view of the laboratories



Interior view of the atrium

SUPPORTED PROJECTS

SUMMER PROGRAM FOR UNDERGRADUATES (SUR/SRP)

For the seventh year running, the ISREC Foundation has supported the internship of five UNIL/CHUV and seven EPFL students in cancer research laboratories. During eight weeks (from July 3 to August 27, 2014), the young biologists or physicians were given the chance to discover the world of research for the very first time; a rewarding experience and the opportunity to establish new contacts on an international level. At the end of the program, on August 26, 2014, the students were invited to present their work during a mini symposium held at the UNIL campus.



Photo: Combined EPFL and UNIL Summer Research Program participants at students' symposium 2014

TOPICS COVERED

ALIBHE NI CHOSGORA

Group Prof. Daniel Constam – EPFL/SV/ISREC

Targeting gene expression of activin-A proprotein convertases in a melanoma cell line

ALYSSA BENJAMIN

Group Prof. Joachim Lingner – EPFL/SV/ISREC

Validation of CEP170 as a telomere-binding protein

DMITRY GORBATCHEV

Group Prof. Melody Swartz – EPFL/SV/IBI
Prox1 expression in lymphatic endothelial cells

HOSSEIN TAHERI

Group Prof. Cathrin Brisken – EPFL/SV/ISREC
Birth control pills and breast cancer risk

SHENG KAI PONG

Group Prof. Pierre Gönczy – EPFL/SV/ISREC
Functional analysis of SAS-5 protein domains in *C. elegans* embryos

LAUREN WATKINS

Group Prof. Jeffrey A. Hubbell – EPFL/SV/IBI
Targeted tumor suppression via protein engineering

PINAK SAMAL

Group Prof. Yann Barrandon – UNIL/CHUV
Exploring Piezo2 expression in whisker Merkel cells during mouse embryonic development

WAAD ALBAWARDI

Group Prof. Vincent Dion – UNIL/CIG
Is the NuRD complex involved in trinucleotide repeat instability?

SARAH ARTHUR

Group Prof. Alexandre Reymond – UNIL/CIG
The function of MAPK3 in the 16p11.2 deletion syndrome

CONSTANTINOS CONSTANTINIDES

Group Prof. Winship Herr – UNIL/CIG
HCF-2 associates with HCF-1c subunit

ELGIN GULPINAR

Group Prof. Tatiana Petrova – UNIL/DEO
Analyzing the cytoskeleton of lymphatic endothelial cells transfected with sifoxc2 RNA

PRITHWIJIT SARKAR

Group Prof. Sophie Martin – UNIL/DMF
Development of an optogenetics system for targeted activation of cell polarity factor Cdc42 in *Schizosaccharomyces pombe*

GRANT

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

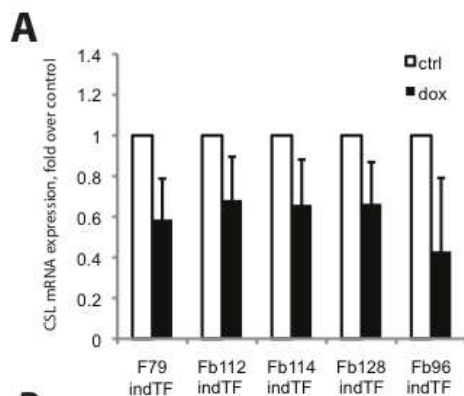
The aim of the project is to test whether alterations in cell-cell communication resulting from down-modulation of Notch signaling may play a role in skin cancer development.

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 third year**

It is very important to understand the regulation of the transcription factor CSL in fibroblasts. This knowledge could help us to find a way to recover CSL expression in CAFs and to act on the microenvironment to limit tumor growth. CAFs, as we have already demonstrated, can be induced by CSL loss. Our goal is thus to understand the actors in CSL regulation.

(A) Fibroblasts from different individuals presenting overexpression of the transcription factor of interest show downregulation of CSL at the RNA level.

(B) Fibroblasts from different individuals presenting overexpression of the transcription factor of interest show downregulation of CSL at the protein level.

The aim of the third year of the project was: 1) to understand the pathways which can regulate CSL; 2) to link these pathways with the response to UVA irradiation and pro-fibrotic signaling; 3) to understand whether differences in CSL regulation may be related to the differences in squamous cell carcinoma occurrence in different human populations.

To answer these questions, we first took advantage of several bioinformatic tools to look at all the single nucleotide polymorphisms (SNPs) in CSL regulatory regions that are present with varying frequencies among different populations. SNPs are basically differences in the DNA sequence that occur in individuals and involve the mutation of one nucleotide into another. Most of these SNPs are common, and there are patterns in the statistical distribution of these SNPs in populations. Normally, the change of one SNP does not affect the correct behavior of cells, but it can induce slight changes that make each individual unique. We have identified several SNPs that are present more frequently in one population than another, first comparing Caucasian and African individuals. Since all of this work was done on publicly available databases, we confirmed the predicted frequencies by sequencing the CSL regulatory regions of individuals of both African and Caucasian origin. We then looked for the predicted transcription factor binding sites that were affected in silico by these SNPs. We found that some of the transcription factors predicted to bind in the CSL regulatory regions and affected by the SNPs are likely responders to cellular stresses. This means that these transcription factors are likely links between UVA exposure (which, as we demonstrated during the second year, has the ability to regulate CSL expression) and CSL downregulation.

Nothing is known about CSL transcriptional regulation, which is why we decided to investigate whether these transcription factors are indeed capable of regulating CSL expression. We started with one of them, and were able to show that its overexpression downregulates CSL at the RNA level, and that silencing of this transcription factor induces CSL transcription.

We are now investigating overexpression and silencing of the other transcription factors we identified. We are also performing chromatin immunoprecipitation (ChIP) experiments to determine whether these transcription factors can really bind to CSL regulatory regions to regulate CSL transcription.

GRANT

GRANT “CANCER AND IMMUNOLOGY”

The role of the Notch receptor in CD4 TH17 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 (N1) and Notch2 (N2) receptor signaling in TH17 cell differentiation and in the development of a TH17 response. The function of TH17 cells and IL-17 in cancer appears to be context-dependent, and was reported to either promote or reduce tumor growth. The role of Notch receptor signaling in TH17 cell differentiation is currently being investigated *in vivo*, using the murine experimental model of B16 melanoma cells and other models that promote a TH17 cell response. In the B16 *in vivo* model, the IL-17 secreted by TH17 cells has been reported to impact on tumor growth. In our experiments, mice carrying a specific T-cell ablation of Notch1 and Notch2 (N1N2 Δ CD4Cre) will be used to identify the role of Notch receptor signaling in TH17 cell differentiation.

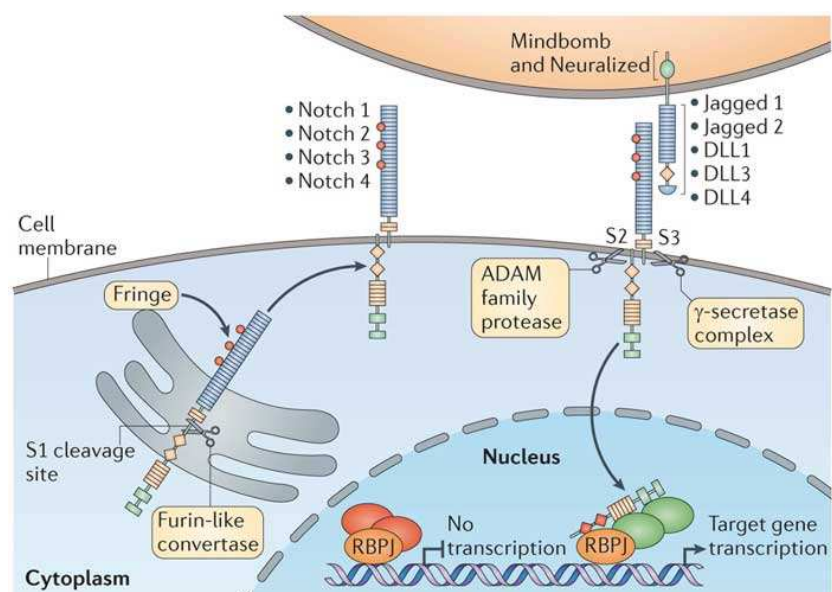
Results after the third year

The role of Notch receptor signaling in TH17 cell differentiation was first investigated *in vitro*. We have shown that N1 and to a lesser extent N2 are expressed on TH17 cells. Furthermore, no compensatory expression of N3 and N4 on TH17 cells was observed in the absence of N1 and N2. Interestingly, in the absence of Notch, reduced IL-17A secretion was observed when low TCR-activating signals were used during *in vitro* TH17 cell differentiation. This suggests that the level of Notch signaling plays a role in the control of the TH17 cell effector function.

To further investigate if Notch receptor signaling influences IL-17A release *in vivo*, we injected N1N2 Δ CD4Cre mice and their respective controls with ovalbumin (OVA) in complete Freund's adjuvant (CFA), an adjuvant reported to promote a TH17 cell response. As we had observed in the B16 melanoma model, N1N2 Δ CD4Cre mice have increased intracellular IL-17A levels in CD4+ T cells following injection of OVA in CFA (Figure 2).

From Radtke F, MacDonald HR, Tacchini-Cottier F, NRI, 2013

Notch signaling is initiated by the ligand engagement of the Notch receptor. There are four Notch receptors (N1-4) and five Notch ligands (delta-like (Dl) 1, 3, and 4; Jagged 1 and 2). In the canonical form, the intracellular domain of Notch goes into the nucleus to a transcriptional repressor RBP-Jk which displaces the co-repressor complex and activates the expression of the Notch target genes.



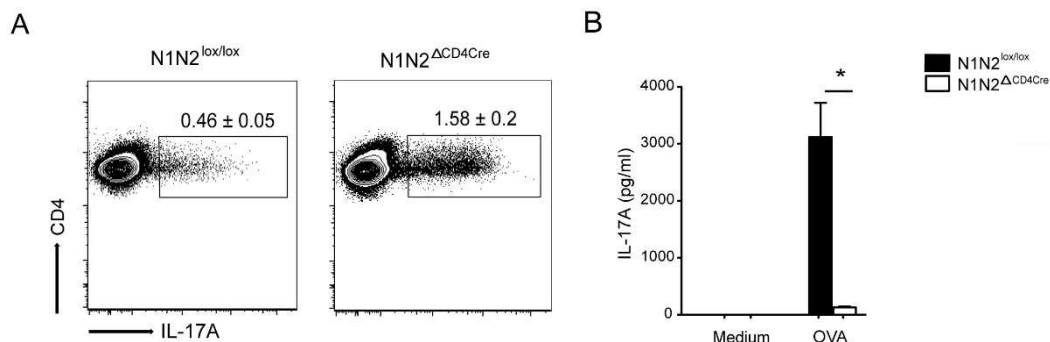
However, after antigen restimulation *in vitro*, N1N2 Δ CD4Cre CD4⁺ T cells secreted significantly reduced levels of IL-17A compared to control mice (Figure 2). Collectively, these data show that Notch receptor signaling plays a critical role in the regulation of TH17 cell effector function *in vivo*, with a specific impact on IL-17A cytokine secretion.

To extend these observations to pathogenic TH17 cells (IL-17A⁺-IFN- γ ⁺ CD4⁺ T cells), another subset of TH17 cells, we also used an adoptive colitis transfer model in which the development of the TH17 cell response was reported to influence colitis disease progression. At the onset of the disease, recipient mice transferred with control and N1N2 Δ CD4Cre CD4⁺ T cells displayed similar colitis development. However, we observed reduced frequency of IL-17A⁺ and IL-17A⁺-IFN- γ ⁺ CD4⁺ T cells in the colon of recipient mice transferred with N1N2 Δ CD4Cre CD4⁺ T cells. Furthermore, a reduced IL-17A cytokine level was measured in supernatants of restimulated cells from the colon of mice transferred with N1N2 Δ CD4Cre CD4⁺ T cells compared to controls. Altogether, our results show that Notch signaling has an impact on the differentiation of TH17 cells, both *in vitro* and *in vivo*.

Future directions

We will investigate how Notch receptor signaling influences cytokine secretion. By means of fluorescence microscopy, we plan to visualize the cellular compartment in TH17 cells in which TH17 cytokines accumulate in the absence of Notch signaling. We will then focus on different target proteins involved in cytokine secretion and investigate whether Notch can regulate their expression. By injecting B16-OVA melanoma cells, we will also determine whether IL-17A secretion in the B16 melanoma model is impaired, in order to evaluate the secretion of IL-17A by N1N2 Δ CD4Cre TH17 cells isolated from tumor-draining lymph nodes (TdLNs) upon OVA restimulation.

Figure 2



N1N2^{lox/lox} mice (control) and N1N2 Δ CD4Cre mice were injected with OVA emulsified in CFA during 9 days. **(A)** Intracellular IL-17A levels were assessed following PMA/Ionomycin restimulation in CD4⁺ T cells. Numbers in representative FACS plots show the frequency of IL-17A⁺ within CD4⁺ T cells \pm SEM. **(B)** 9 days post-injection of OVA/CFA, dLN CD4⁺T cells were isolated and restimulated during 72 hours with or without OVA (medium). Mean values of cytokine levels of IL-17A \pm SEM are shown.

GRANT

GRANT “CANCER AND IMMUNOLOGY”

Crosstalk between T lymphocytes and melanoma cells

This “allocated grant”, amounting to CHF 40'000.- per year, was awarded to Natalie Neubert in January 2015 for one year with the support of the Zwillenberg Foundation

Natalie Neubert is working in Professor Daniel Speiser's laboratory, 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 powerful anti-tumor immune cells, because they can infiltrate the tumor microenvironment and destroy tumor cells. However, even following immunotherapy, the anti-tumor immune response often does not lead to complete tumor eradication and tumors frequently relapse.

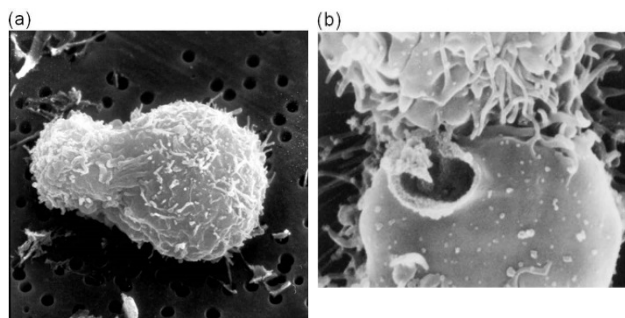
How can tumor cells survive and progress even in presence of tumor-specific CTLs? We are studying the interaction between CTLs and their target melanoma cells. Specifically, we are interested in the rapid reactions of human melanoma cells to immune attack.

Results after three years

To study CTL-tumor cell interactions, we have set up a co-culture system of melanoma cell lines with melanoma-specific CTLs. Melanomas develop from melanocytes, pigmented cells mostly found in the skin but also in the eye and inner ear. They express melanoma-specific antigens, such as the melanoma differentiation antigen MelanA. This antigen can be recognized by CTLs via their T cell receptor.

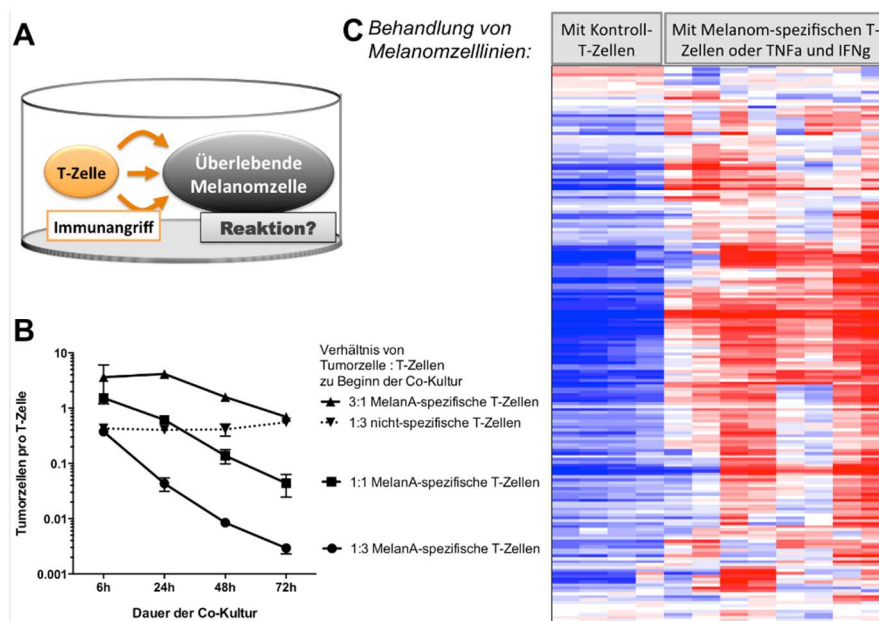
Co-cultures were set up for four different melanoma cell lines. To test if the co-culture is a valid system to investigate CTL-melanoma cell interactions, we analyzed a series of parameters of which the behavior is known. As expected, melanoma cells reacted to CTL attack by increasing HLA-Class I expression in all four co-culture systems, whereas the expression of the target antigen MelanA was decreased, suggesting that the co-culture is a trustworthy model.

Next, the co-cultures were screened for changes between untreated melanoma cells and melanoma cells having survived the presence of melanoma-specific CTLs. A genome-wide mRNA analysis showed that hundreds of genes had changed after co-culture. Three melanoma cell lines behaved similarly, indicating that the changes are not patient-specific.

**Electron microscopy**

(A) Tight interaction of the T cell (left) with the large tumor cell (right). **(B)** A lethal hole in the tumor cell (bottom), punched by the T cell (top) already detached and on its way to other tumor cells (ASM MicrobeLibrary©Young).

The 185 most promising genes were chosen for further mRNA-based analyses. CTLs with irrelevant antigen specificity were used as a negative control to identify changes induced by interactions with melanoma-specific CTLs and not by interactions with irrelevant CTLs. The expression of over 80 of those genes was changed in co-cultures with melanoma-specific CTLs but not in co-cultures with control CTLs, demonstrating the need for an antigen-specific interaction between the CTL and the melanoma cell. Interestingly, treatment of melanoma cells with TNF α and IFN γ , two cytokines that are typically secreted by CTLs after interaction with their target cells, provoked reactions similar to treatment with melanoma-specific CTLs. Consequently, factors secreted by CTLs attacking melanoma cells can influence neighboring melanoma cells and direct cell-cell contact might not be necessary to induce many of the observed changes.



- (A) Working model for co-culture of melanoma-specific CTLs with melanoma cell lines.
 (B) Development of tumor cell: CTL ratio during the co-culture. An unspecific CTL, that is not able to recognize the tumor cells, was used as a negative control.
 (C) Gene expression of 185 selected genes in melanoma cells treated with control CTLs, melanoma-specific CTLs or TNF α and IFN γ . Each column represents one melanoma cell line with the indicated treatment. Each line indicates the expression changes of one gene (in comparison with untreated melanoma cells). Color code: red indicates genes that are upregulated in treated melanoma cells compared to untreated melanoma cells. White shows slightly upregulated genes. Blue indicates genes that are unchanged or downregulated.

Conclusion

We set up a co-culture system of human CTLs and melanoma cells to study rapid reactions of melanoma cells to immune attack. Treatment with melanoma-specific CTLs or TNF α and IFN γ , but not with negative control CTLs, induced important changes in melanoma cells.

Our findings support a dynamic interplay between CTLs and melanoma cells, driving resistance mechanisms that may involve environmental factors and cells. We are now focusing on functional studies of selected candidates identified in the above-mentioned mRNA screen.

The outcome of this project will likely contribute to our understanding of immune-related mechanisms in cancer progression, and may help improve therapeutic strategies.

GRANT

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 involved in plasma cell differentiation, 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). Additionally, gene expression data suggest that XBP1 target genes are upregulated in activated B-cell-like (ABC) lymphoma as compared to germinal center B cell (GCB) lymphoma. ABC and GCB are two specific subsets of diffuse large B cell lymphoma (DLBCL) (4). All together, these observations suggest a dual role of XBP1 in progression and treatment response of B cell malignancies.

My project is aimed at elucidating the significance of the UPR signaling pathways in tumors by first focusing on the role of the IRE1-XBP1 signaling branch in diffuse large B cell lymphoma.

Previously obtained results

In the first year report, I showed that the ER-stress sensor IRE1 is downregulated in GCB lymphoma as compared to ABC DLBCL. Consequently, the production of XBP1, a potent downstream transcription factor, was impaired in GCB cell lines after treatment with ER stress-inducing drugs.

During my second year, I showed that in contrast to the dramatic difference in IRE1-XBP1 expression, the PERK-ATF4 branch is equally expressed and functional in both ABC and GCB DLBCL subtypes. These data indicated that GCB cells do not exhibit a general defect in the ER signaling platform, but rather a specific downregulation of the IRE1-XBP1 signaling branch. The observations mentioned above 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.

Results obtained in the third year : Our results indicate that prolonged expression of XBP1 in GCB cells leads to decreased survival of tumor cells *in vitro*, suggesting that IRE1-XBP1 deficiency could be a feature acquired by GCB DLBCL in order to facilitate tumor growth. Considering the well-described role of XBP1 in promoting plasma cell differentiation, we hypothesized that IRE1-XBP1 downregulation in GCB DLBCL cells contributes to differentiation arrest of this tumor type at the germinal center B cell stage.

Next, we assumed that due to the specific inhibition of the IRE1-XBP1 pathway, GCB DLBCL cells predominantly rely on the PERK-ATF4 branch under conditions of ER stress. The PERK-ATF4 signaling pathway is another UPR branch activated under stress conditions (Figure 1). To test this hypothesis, we treated ABC and GCB DLBCL with ER stress-inducing drugs in presence or absence of PERK inhibitor. We demonstrated that inhibition of PERK-ATF4 signaling makes GCB cells hypersensitive to ER stress, while the same treatment does not affect ABC DLBCL survival. The data obtained so far indicate that IRE1 deficiency is a hallmark of GCB DLBCL tumors and could contribute to their increased sensitivity to ER stress-inducing drugs. Moreover, IRE1-XBP1 deficiency renders GCB DLBCL cells dependent on PERK-ATF4 signaling during conditions of ER stress. All together, these results may provide us with new therapeutic strategies aimed at the specific targeting of the GCB DLBCL subtype.

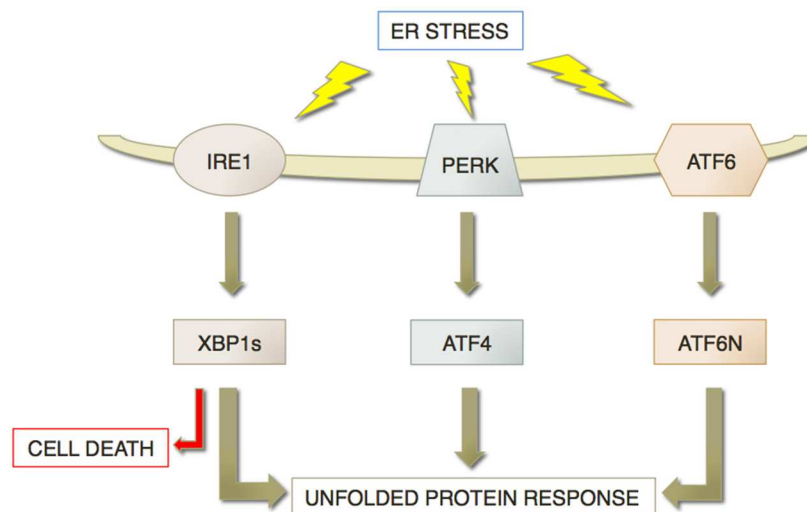


Figure 1: ER stress signaling platform

Stress within the ER is detected by sensor proteins IRE1, PERK and ATF6, whose activation triggers three signaling cascades leading to an adaptation response that reduces the ER stress and restores homeostasis via the activation of the unfolded protein response (UPR). Deregulation of ER-signaling pathways was observed in different types of tumors. The role of XBP1 and the UPR in diffuse large B cell lymphoma (DLBCL), a B cell malignancy found in around 40% of all lymphoma patients, has not yet been investigated. My project is aimed at elucidating the role of UPR signaling pathways in tumors by focusing first on the role of XBP1 in DLBCL. My data demonstrate that the IRE1-XBP1 pathway is downregulated in germinal center DLBCL and that reconstitution of XBP1 in this DLBCL subtype leads to tumor cell death.

References

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GRANT

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 remain 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 β 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 the second year, I used the biosensor CLIPv4, previously developed in the lab, to quantify PCSK activities in specific subcellular compartments in normal and cancer cells. The biosensor consists 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 (Fig. 1). The two fluorophores were chosen for their capability to perform Förster resonance energy transfer (FRET). Measuring FRET reveals what fraction of the biosensor has been cleaved. While maximal FRET values are detected in the absence of cleavage, reduced FRET values indicate the presence of elevated proprotein convertase activity. Until now, PCSKs have been thought to cleave the majority of their substrates in the trans-Golgi network. By contrast, my analysis of compartment-specific CLIPv4 variants in cultured cells suggests that PCSK activities are much higher in post-Golgi compartments. To quantify PCSK activities at the subcellular level, I measured FRET efficiency of CLIPv4 in the B16F1 mouse melanoma cell line that endogenously expresses the PCSK family members Furin and PC7. To determine the maximum FRET signals possible in each compartment, I also introduced analogous compartment-specific variants of the corresponding cleavage mutant biosensor mCLIPv4. These values were then used to normalize the FRET values of cleavable CLIPv4. For example, in late endosomes, I thus found that CLIPv4 loses 60-70% of FRET efficiency compared to mCLIPv4. To elucidate which of the two PCSKs present is responsible for the cleavage, I performed a similar analysis in B16F1-F2 or B16F1-G7 subclones, which I had treated with specific single guide RNAs and CRISPR/Cas9 to specifically mutate PC7 or Furin, respectively. While CLIPv4 cleavage was indistinguishable in parental B16F1 cells and in the PC7 mutant B16F1-F2 subclone, B16F1-G7 cells lacking Furin showed a markedly increased FRET efficiency, indicating that cleavage of the biosensor in late endosomes is mediated by Furin (Fig. 2). This study shows that our biosensor CLIPv4 is suitable to quantify PCSK activities using FRET and to map PCSK activities at subcellular resolution in cancer cells.

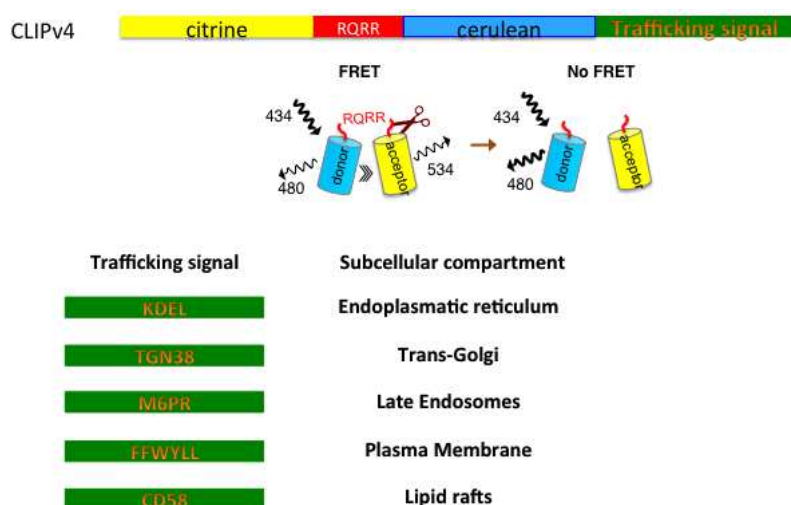
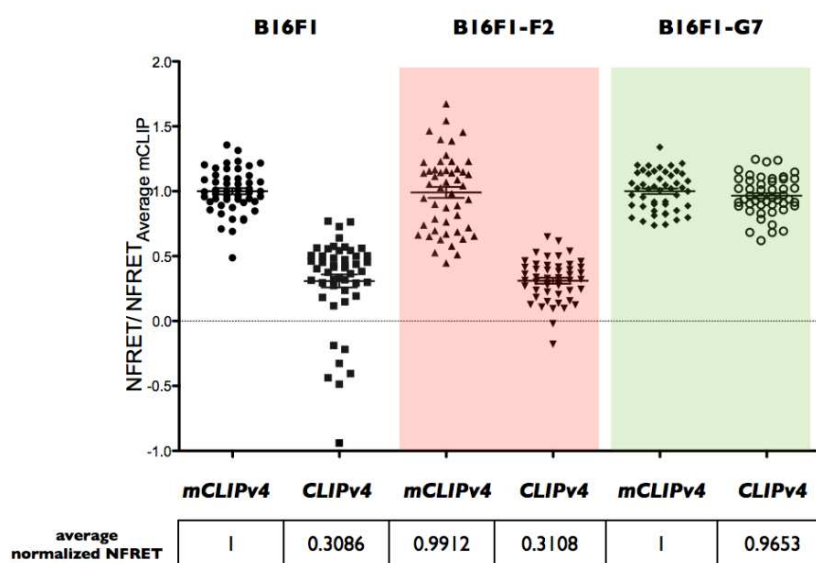


Figure 1: Design of cell-linked indicator of proteolysis (CLIPV) biosensor variants. Cleavage of the linker RQRR between the donor and the acceptor inhibits FRET. The table indicates the trafficking signals used to target the biosensor to the subcellular compartment of interest. The KDEL sequence for the endoplasmic reticulum, the TGN38 (TM domain and cytosolic tail of the human TGN38 protein) sequence for the TGN network, the M6PR (TM domain and cytosolic tail of bovine cation-dependent mannose 6-phosphate receptor) sequence for late endosomes, the FFWYLL (mutant TM domain and cytosolic tail of bovine cation-dependent mannose 6-phosphate receptor) sequence for the plasma membrane and the CD58 (GPI anchor of the human CD58 protein) sequence for lipid raft domains.

Figure 2: FRET efficiencies of CLIPv4 and corresponding cleavage mutant mCLIPv4 constructs in late endosomes of B16F1 cells, measured by sensitized emission.

Normalized FRET efficiency (NFRET) was estimated as described (Xia et al., 2001). The average normalized NFRET values of mCLIPv4 and CLIPv4 are indicated in the table.



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GRANT

GRANT “MOLECULAR LIFE SCIENCES”

The 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

Non-small cell lung cancer (NSCLC) is the leading cause of cancer deaths worldwide. The epithelial-to-mesenchymal transition (EMT) is a developmental program that is often reactivated in cancer to promote tumor progression. The aim of my project is to improve the understanding of the contribution of EMT to the development and progression of NSCLC. Specifically, the role of two transcription factors (TF) known to induce EMT, ZEB1 and Snail, is being investigated. One key aspect is to explore a possible connection between EMT and the glucose metabolism of the cancer cell.

Results*The study of EMT in the cell*

For experiments in the laboratory, we use cell lines that originate from NSCLC patients. We have previously characterized the epithelial and mesenchymal features of 10 cell lines and ranked them according to their epithelial and mesenchymal status. I have now generated cell lines in which the expression of ZEB1 or Snail can be induced by adding antibiotics to the culture medium, resulting in an EMT of the cells. This will enable us to assess the impact of each TF and to compare their functions.

The study of EMT in mice

To study EMT in mouse lung tumors, I use a sophisticated system, similar to the one described for the cell line experiments, which enables us to induce the expression of ZEB1 or Snail directly in the mouse lung tumors, at tumor initiation or during tumor progression.

Glucose metabolism

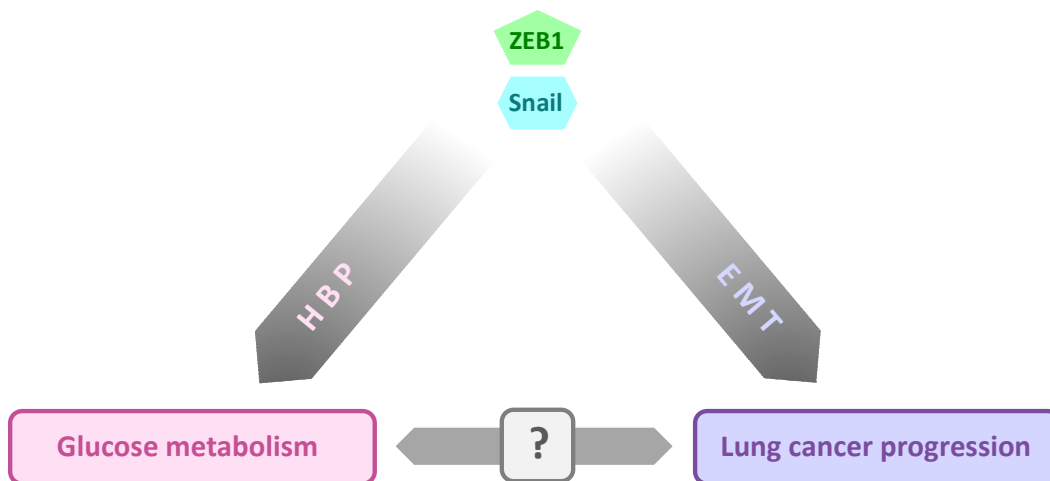
We have recently discovered a link between glucose metabolism and EMT. We have shown that the neuronal glucose transporter GLUT3 is part of the reactivated EMT program in human NSCLC and that high expression of GLUT3 is associated with a poor prognosis. The TF ZEB1 directly activates the GLUT3 gene and hence increases GLUT3 expression. These results are part of a recently published article in which I am a co-author (Masin *et al.* 2014).

The hexosamine biosynthesis pathway

In order to discover additional metabolic players of the EMT program, we have analyzed gene expression data from NSCLC patients and have identified another metabolic gene that codes for glutamine:fructose-6-phosphate amidotransferase 2 (GFPT2). GFPT2 is an important enzyme of the hexosamine biosynthesis pathway (HBP). The HBP is a metabolic pathway which produces a substrate for protein modifications that are essential for signal transmission within the cell. Among other functions, this modification can stabilize Snail and thereby contribute to an EMT. As for GLUT3, we have found that a high expression of GFPT2 predicts a poor prognosis in NSCLC. Additionally, induction of ZEB1 or Snail led to an increased GFPT2 expression.

Summary

During my first year, I have established two complementary systems to study EMT, both in human NSCLC cell lines and in a mouse model of NSCLC. I have identified GFPT2 as a potential link between glucose metabolism and EMT. Preliminary experiments indeed indicate that GFPT2 and the HBP might play a role in EMT and are therefore very interesting to further investigate in the context of NSCLC progression.



Working hypothesis

The TFs ZEB1 and Snail are known inducers of EMT and thus probably contribute to the progression of lung cancer. Furthermore, the TFs potentially influence the glucose metabolism of the cancer cell, with the activation of the HBP as a possible example. However, these effects on lung cancer progression and glucose metabolism are probably not isolated processes, but they might be connected and depend on each other. Our goal is to elucidate this intriguing connection, in order to provide insight into the mechanism of cancer progression.

Reference

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CHAIR

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

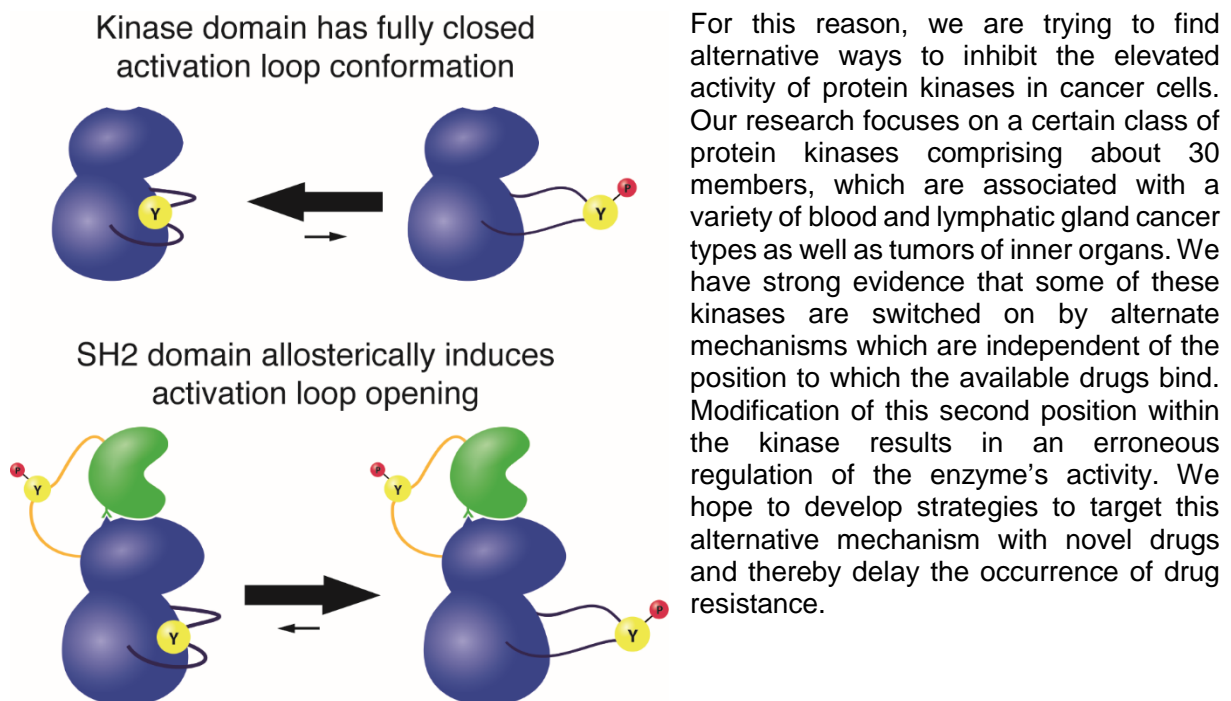
It was awarded to the research group of **Prof. Oliver Hantschel** (EPFL/SV/ISREC)

Introduction

The tumor cells of cancer patients contain a variety of modifications in their genetic material. In most cases, these changes result in the production of structurally modified proteins or abnormal amounts thereof.

Many cancer-causing proteins are enzymes that transfer phosphate groups onto other proteins, thereby transmitting signals for cancer progression. These enzymes are called protein kinases. Kinases function as molecular switches and adopt a predominantly inactive conformation in normal cells. In contrast to normal conditions, kinases are continuously activated in cancer cells, as a consequence of the genetic modifications. Within the last ten years, a total of 25 new drugs, which bind and block these activated kinases and therefore limit tumor growth, have been developed by the pharmaceutical industry and approved for clinical use. In addition to monoclonal antibodies, these protein kinase inhibitors have become the most important examples of targeted cancer therapy. They generally possess a high efficacy and are well tolerated by the patient.

Unfortunately, the success of protein kinase inhibitors is often limited due to the development of resistance.



The BCR-ABL kinase domain (blue) has a predominantly inactive activation loop conformation (upper panel). Upon formation of the SH2-kinase interface, the equilibrium is shifted towards a predominantly open activation loop (lower panel).

Results

The protein kinase, for which this alternative regulation mechanism has been observed in our lab, is BCR-ABL. This very active protein kinase causes chronic myeloid leukemia (CML). For the last ten years, CML patients have been treated with the highly specific BCR-ABL inhibitor imatinib (trade name: Gleevec, by Novartis). However, as mentioned above, the development of resistance in some of the patients results in disease progression.

We have thus elucidated the molecular details of the alternative regulation mechanisms of BCR-ABL. We have produced parts of the protein in a purified form and characterized their biochemical properties in detail. This approach led to the discovery of specific differences in the three-dimensional structure of the over-activated (cancer-causing) and the less activated (non-cancerous) conformation of the BCR-ABL protein.

The results of this study were recently published in the journal Nature Communications (Lamontanara et al., 'The SH2 domain of ABL kinases regulates kinase autophosphorylation by controlling activation loop accessibility', Nat. Commun. 5, 5470). Our next goal within this project is the establishment of methods to allow a high-throughput screening of large drug libraries in order to find new inhibitors for BCR-ABL which target the alternative mechanism of kinase regulation. We expect to find a novel approach for combination therapy together with imatinib, in order to prevent resistances and ameliorate the general tolerance of the therapy.

With our research, we hope to make a contribution to the development of durable therapies for cancer patients with efficient and specific drugs.

ISREC CHAIR "FUNDAMENTAL 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 a UNIL/CHUV research group

Assistant tenure track professor to be nominated

The first results will be available in 2015

CHAIR

ISREC CHAIR “TRANSLATIONAL ONCOLOGY”**Decoding the genetics of lymphoma for the development of new therapies**

This chair endowed with CHF 500'000.- per year for a period of six years was allocated in November 2014

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

The Oricchio laboratory at ISREC-EPFL opened in November 2014. With the support of the ISREC Foundation, I have been able to recruit a senior technician and a junior postdoc with experience in cancer biology to start our research activity.

Introduction

Research in the Oricchio laboratory focuses on the genetics of lymphoma and its translation into new therapies. Lymphoma is a heterogeneous disease characterized by multiple genomic alterations. Our goal is to define the functional role of recurrent genetic lesions in lymphomagenesis. We will combine genomic analyses of human tumors with *functional in vivo* studies. We will also use mosaic models of lymphomas to functionally annotate genes of interest identified by the genomic analyses and to perform pre-clinical treatment studies.

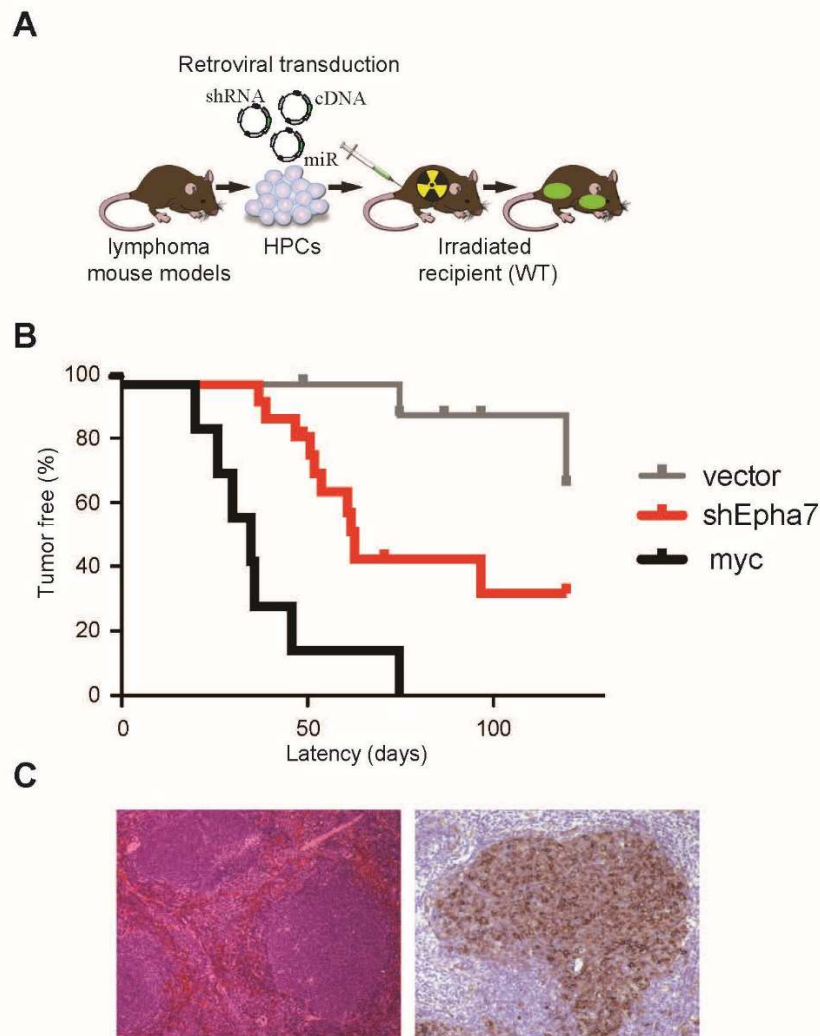
Detailed description of the project

Initially, we will analyze lymphoma patient samples by RNA sequencing to quantitatively measure cancer-associated variations in gene expression and specific isoform levels, as well as to identify potential novel gene fusions. We will integrate these data with mutations and chromosomal aberrations to provide unprecedented insights into the genomics of lymphoma. We will complement the genomic analyses with functional screenings to define the phenotypical contribution of these alterations to lymphomagenesis. This step is critical to the design of *in vivo* functional studies.

Next, we will use genetically engineered mouse models of lymphoma to study the genetics and pathology of the disease. These murine models retain key human features. We will exploit them to dissect the impact of recurrent genomic alterations on lymphoma initiation and transformation *in vivo*.

Our ultimate goal is to use our genetic and biological studies to design new therapeutic strategies. Frequent genomic alterations can influence the patient response to current therapies. Mutated genes can promote mechanisms of resistance and their activity can be blocked by using selective inhibitors.

To test our hypotheses, we will use highly controlled experimental systems that resemble the design of clinical trials in a physiological context. We will test combination therapies in genetically defined tumors, we will directly compare the impact of different genetic lesions on therapy and we will measure the effect of tumor intrinsic heterogeneity on the treatment.



Functional *in vivo* studies using a murine model of lymphoma

(A) Schematic of the adoptive transfer strategy that enables us to quickly define the role of genetic lesions in lymphomagenesis and progression *in vivo*. (B) Representative data indicating how distinct genetic lesions affect tumor latency *in vivo* (myc = c-Myc, shEpha7 = short hairpin RNA against Epha7, vector control). (C) Illustrative histologies of murine lymphomas stained with HE (left) and for PNA (right).

Publications

1. Oricchio E, Nanjangud G, Wolfe AL, Schatz JH, Mavrakis KJ, Jiang M, Liu X, Bruno J, Heguy A, Olshen AB, Socci ND, Teruya-Feldstein J, Weis-Garcia F, Tam W, Shaknovich R, Melnick A, Himanen JP, Chagant R.S.K., and Wendel HG. *Eph- Receptor A7 is a soluble tumor suppressor in follicular lymphoma*. Cell 147-3 554-564 (2011).
2. Oricchio E, Ciriello G, Schatz JH, Jiang M, Heguy A, Viale A, de Stanchina E, Teruya-Feldstein J, Sander C, Wayne T, Seshan VE, Chaganti RSK, Wendel HG. *Frequent disruption of the RB pathway in indolent follicular lymphoma suggests a new combination therapy*. J Exp. Med. (2014) Jun 30; 211(7):1379-91.
3. Oricchio E, Papapetrou EP, Lafaille F, Ganat YM, Kriks S, Mark WH, Teruya-Feldstein J, Huse JT, Reuter V, Sadelain M, Studer L, Wendel HG. "A cell engineering strategy to enhance the safety of stem cell therapies". Cell Report (2014).

FUNDS

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 awarded to **Dr. Olivier Preynat-Seauve** (Laboratory for Immunohematology, University Hospital of Geneva) in June 2011 for three years

Introduction

MicroRNAs (miRNAs) are an exciting and promising potential target for the development of new treatments against tumors. miRNAs are small molecules that regulate high numbers of genes. Consequently, they represent a key molecular checkpoint in the control of crucial biological processes. In order to further the understanding of glioblastoma biology and to move towards the discovery of new therapeutic targets, new cellular tools that more closely model the tumor environment *in vivo* in humans are clearly needed. Indeed, the lack of relevant models for glioblastoma is one of the major limitations in drug discovery. For this reason, we have developed an *in vitro* model of glioblastoma development within brain-like human tissue. This model is based on a combination of patient tumor cells and brain-like tissue engineered from human embryonic stem cells. Our results describe a tumor cell mass growing *in vitro* that exhibits a high degree of similarity to the *in vivo* cancer development in patients. We have therefore taken advantage of this system to analyse the miRNAs involved in the disease. The main objectives were to identify: (i) miRNAs induced or upregulated when the tumor interacts with the brain-like tissue and (ii) miRNAs specifically expressed by glioblastoma patients (and not by healthy patients).

Accomplished work

Using this approach, combined with the analysis of patient biopsies, we have identified miRNAs that could interfere with disease progression.

We have observed that some miRNAs are specifically induced or repressed when brain-like tissue interacts with tumors. Using public databases (Human Cancer Genome Atlas), we have shown that 31 (6%) of these miRNAs are statistically and significantly correlated to patient survival. Among them, miR-494, -892a, -1293 and -340 emerged as the most interesting ones for the following reasons:

- Some are overexpressed in cancer patients and are induced only when the tumor cells interact with nervous tissue (miR-494, -1293).
- Some of them have not been previously described (miR-892a, -1293, -340).
- miR-340 is downregulated (low expression) and appears to be an important miRNA in the overall survival of glioblastoma patients.

In vitro experimental introduction of these miRNAs in cancer cells significantly decreased these cells' activity compared to control conditions.

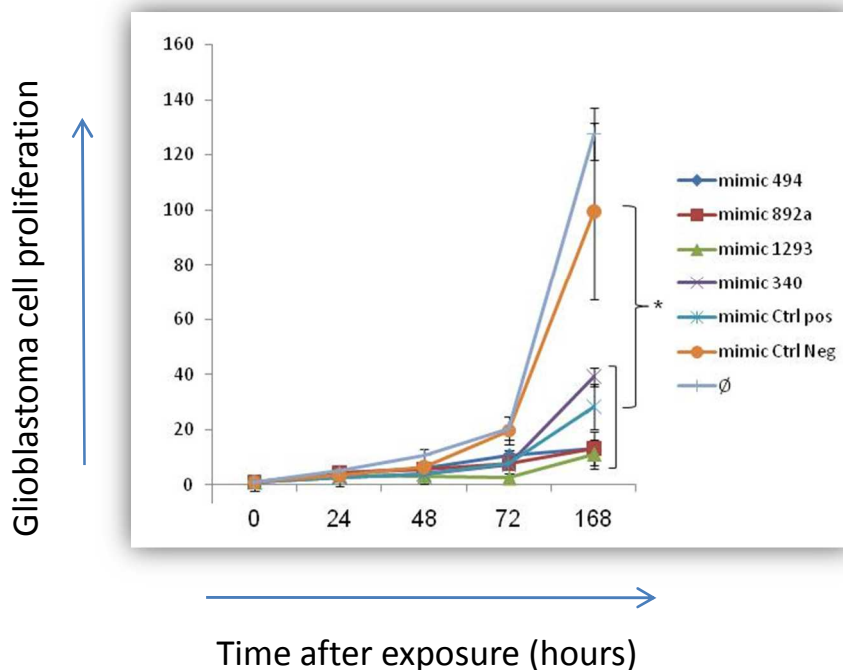
Global conclusion on the project

The initial project consisted in the development of an innovative tissular model to study glioblastoma *in vitro*. The significant progress made during this development allowed the discovery of two additional insights which contribute to the understanding of the disease:

- (i) Exclusion of a possible viral etiology of the disease, a topic which has been highly debated by the scientific community.
- (ii) Identification of miRNAs specifically induced by the tumor/host interaction and possibly active in biological tumor processes.

Two articles describing these observations have been published in international journals: Cosset E, Petty TJ, Dutoit V, Cordey S, Padioleau I, Otten-Hernandez P, Farinelli L, Kaiser L, Bruyere-Cerdan P, Tirefort D, Amar El-Dusouqui S, Nayernia S, Krause KH, Zdobnov EM, Dietrich PY, Rigal E, Preynat-Seauve O. Comprehensive metagenomic analysis of glioblastoma reveals absence of known virus despite antiviral-like type I interferon gene response. *Int J Cancer*. 2013 Dec 17.

Nayernia Z, Turchi L, Cosset E, Peterson H, Dutoit V, Dietrich PY, Tirefort D, Chneiweiss H, Lobrinus JA, Krause KH, Virolle T, Preynat-Seauve O. The relationship between brain tumor cell invasion of engineered neural tissues and *in vivo* features of glioblastoma. *Biomaterials*. 2013:8279-90.



Proliferation of glioblastoma cells exposed to miR-494, -892a, -1293, -340, negative (Neg) and positive (pos) controls. Neg are miRNAs without any biological activity. Pos are miRNAs that are known to decrease cell proliferation. ∅ represents the cells without any miRNA.

FUNDS

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

The gastrointestinal stromal tumor (GIST) is the most common gastrointestinal sarcoma. In 70-80% of all cases, it is characterized by an oncogenic KIT mutation, which is now targeted by imatinib mesylate (IM) that markedly improves the overall survival of GIST patients (1). IM has a direct effect on the GIST tumor, but also indirect immunostimulatory effects on T and natural killer (NK) cells. Indeed, IM activates the dendritic cells (DC)/natural killer cells cross-talk and thereby the function of NK cells (2, 3), which depends on the transcription of the NKp30 isoforms, leading to different biological anti-tumor responses (4). In addition, we have demonstrated by immunohistochemistry that NK cell infiltrates predict the progression-free-survival (PFS) of localized GIST patients (5). IM was also shown to inhibit the IDO enzyme of GIST tumor cells, thus reducing the number of regulatory T cells and allowing the increase of effector CD8⁺T cells with a favorable anti-GIST immunity (6).

Despite its effectiveness, IM is rarely curative. This has prompted us to investigate immune biomarkers of GIST prognosis to better guide therapeutic decisions.

Results**NKp30 receptor isoform transcription and the levels of expression of these isoforms predict the survival of metastatic GIST patients**

NKp30 is a cytotoxic receptor expressed on NK cells that plays a role in tumor cell recognition and DC/NK cell cross-talk. There are three major NKp30 isoforms, each of which presents a specific intra-cytoplasmic domain: NKp30a, NKp30b and NKp30c. NKp30a and b are TH1-like (IFN γ and TNF α), while the NKp30c isoform induces the production of the immunosuppressive cytokine IL-10. The predominant transcription of the NKp30c isoform, or a low ratio between the NKp30b and NKp30c isoforms (low RBC), impacts the prognosis of metastatic GIST patients in a test cohort (ref. 4 and Figure 1A) and, as we have now validated, in a validation cohort (Figure 1B, pooled cohort in Figure 1C). In addition, we have found that the levels of NKp30 isoform expression predict overall survival of metastatic GIST patients in test and validation cohorts (pooled cohort shown in Figure 1D). Combining the NKp30 isoform ratios and the levels of expression highlighted a group of patients with a poor prognosis (Figure 1E) that could benefit from immune-based therapy aiming at increasing the levels of NKp30 expression.

B7-H6 and Bat-3, soluble NKp30 ligands, are biomarkers of progression-free survival in metastatic GIST patients

We next investigated one of the immune escape mechanisms by measuring the release of soluble NKp30 ligands (sB7H6 and sBat-3), soluble NKG2D ligand (sMIC) and as a control soluble thrombospondine and osteopontine, in the serum of metastatic GIST patients. Soluble B7H6 was detected in the sera of GIST patients at diagnosis, predominantly in GIST tumor-bearing patients. The concentration decreased post-IM, suggesting the release and/or the shedding of sB7H6 by GIST tumors. In contrast, the levels of sBat-3 increased following IM, corresponding to the IM-induced apoptosis of the GIST tumor. The presence of either sB7H6 or sBat-3 in the sera of patients at diagnosis predicted the progression-free survival of metastatic GIST patients (Figure 1F, 1G and combined in 1H). In contrast, sMIC was a good prognostic factor for GIST survival, while thrombospondine or osteopontine had no impact on GIST PFS (not shown).

In conclusion, NKp30 isoform ratios and expression as well as soluble NKp30 ligand release in the serum at diagnosis represent valuable biomarkers of GIST patient prognosis, which could provide better therapeutic guidance. These findings prompt us to assess new combined immunotherapeutic strategies to promote NK cell activity, such as increasing the expression of NKp30 isoforms.

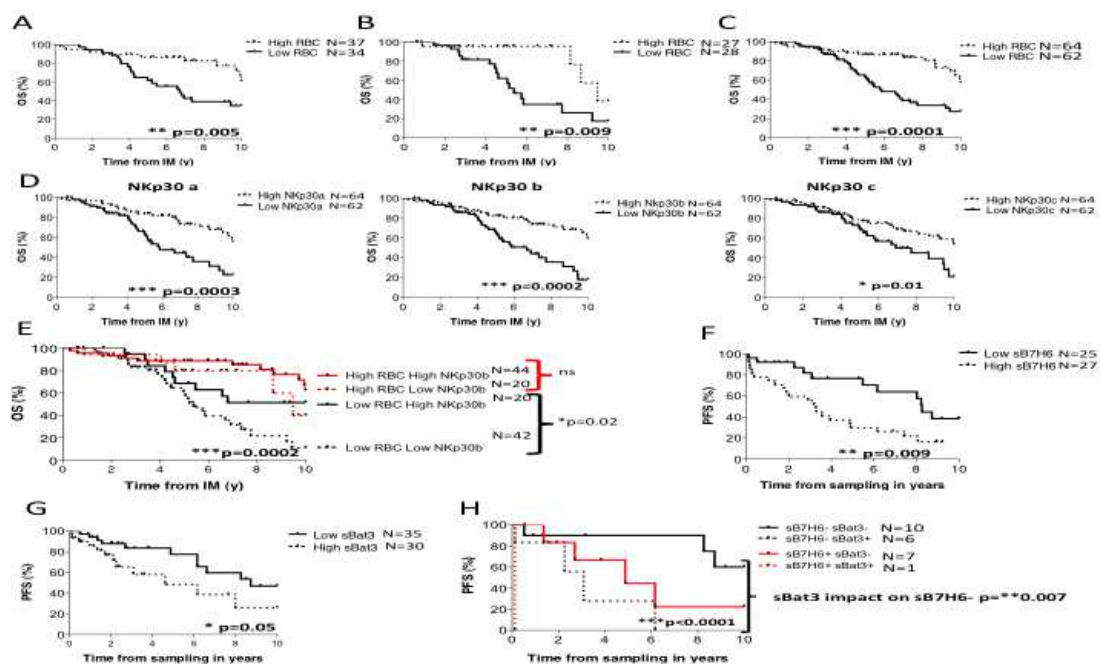


Figure 1: NKp30 isoform transcription and soluble NKp30 ligands (B7H6 and Bat-3) predict metastatic GIST patients' clinical outcome.

The transcription ratio between the NKp30b and the NKp30c isoforms (low RBC) predicts overall survival of GIST patients in a test cohort of N=71 (A), a validation cohort of N=55 (B) and a pooled cohort (N=126, C). In addition, the levels of transcription of NKp30a (D, left panel), NKp30b (D, middle panel) and to a lesser extent NKp30c (D, right panel) also predict overall survival in metastatic GIST patients (test and validation pooled cohort N=126). Combined NKp30 isoform RBC ratio and levels of transcription are shown in panel (E). Soluble NKp30 ligands sB7H6 (F) and sBat-3 (G) or combined sB7H6 and sBat-3 (H) detected in sera of metastatic GIST patients at diagnosis predict progression-free survival.

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FUNDS

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

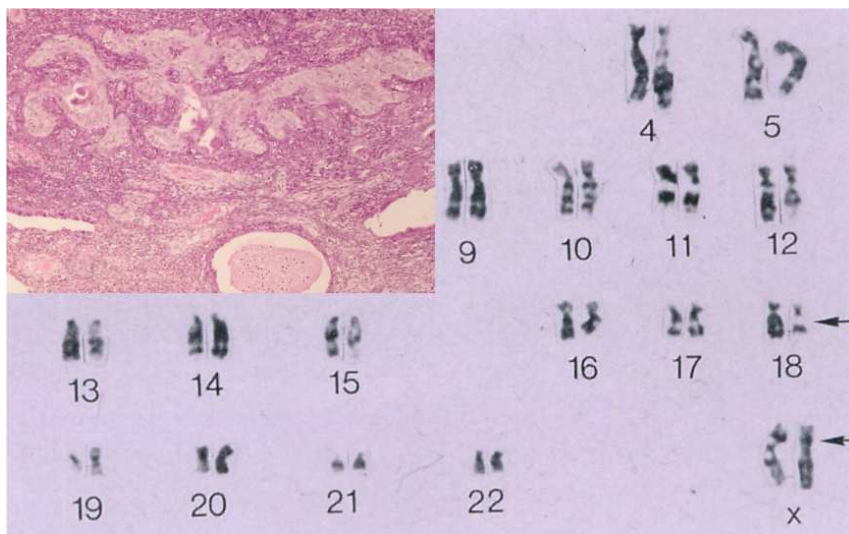
We have undertaken studies aimed at identifying the cell of origin of a variety of sarcomas, with the goal of elucidating the oncogenic events that lead to primary cell transformation and subsequent development of full-fledged tumors with the ability to metastasize. We have shown that bone marrow-derived mesenchymal stem cells (MSC) are the 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 the osteosarcoma and the synovial sarcoma, also originate in MSC subsets.

Our observations have led us to identify mechanisms whereby MSCs become transformed to develop different types of sarcoma. We have found that the fusion gene EWS-FLI1, characteristic of Ewing's sarcoma and arising as a result of a specific chromosomal translocation, induces a series of epigenetic modifications in MSCs 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 MSCs 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. We are using similar approaches to address the pathogenesis of other sarcomas.

Results after the third year

In 2014, we pursued five major avenues of sarcoma research. The first was the completion of our work on Ewing's therapy, namely, the study of a combination of targeted therapy aimed at eliminating cancer stem cells and conventional therapy aimed at the tumor bulk. We had shown earlier 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 have assessed the effect of a combination of enoxacin and doxorubicin on primary Ewing's sarcoma xenografts in immunocompromised mice. We have shown that a combination of enoxacin and doxorubicin (the standard of care cytotoxic drug in Ewing's sarcoma) is far more effective in preventing tumor growth than either drug alone. As enoxacin has long been approved for the treatment of infections, we are proceeding to launch clinical trials of the combination therapy in Ewing's sarcoma. Our work on the combination treatment has recently been published in *Cancer Research* (see below).

The second avenue of research also focuses on Ewing's sarcoma and comprises a comprehensive assessment of epigenetic changes that drive or maintain the CSC phenotype. We have purified CSCs from several primary Ewing's sarcoma samples and, using chromatin immunoprecipitation followed by sequencing (ChIP-seq), have begun systematic histone modification assessment in CSCs compared to the tumor bulk. This work is intended to identify epigenetic mechanisms that lead to CSC maintenance and specify CSC behavior, in addition to changes in miRNA maturation. In collaboration with a former MD PhD student, Nicolo Riggi, we have, during the past year, identified mechanisms whereby the EWS-FLI-1 fusion protein can act as both an inducer and a repressor of selected gene expression and thereby contribute directly to MSC reprogramming. This work has been published in *Cancer Cell* (see below).



Biphasic synovial sarcoma with reciprocal chromosomal translocation t (X; 18)

Biphasic synovial sarcoma displaying an epithelioid (arrow) and mesenchymal phenotype. Also shown (arrows) is the signature chromosomal translocation t (X; 18) that gives rise to the SYT-SSX fusion gene.

The third avenue involved analyzing the effect of expressing fusion genes associated with other sarcomas in human adult and pediatric mesenchymal stem cells. 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. This has led to the study of the pathogenesis of synovial sarcoma (SS), 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 have gathered 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, thereby participating in CSC maintenance. We have begun to understand the molecular mechanisms whereby SYT-SSX alters Wnt signaling in a way that ensures SS cell survival and tumor-initiating capacity.

The fourth and fifth avenues of research focus on the assessment of tumor cell heterogeneity and tumor-host interactions in sarcomas that are not associated with defined chromosomal translocations. We are studying myxoid fibrosarcoma and leiomyosarcoma using ChIP-seq and RNA-seq on primary tumor cells, and are determining the composition of the tumor stroma in both tumor types.

Publications

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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)

Introduction

Cancer immunotherapy aims at mobilizing the body's immune cells to fight against tumor cells in a highly specific manner and to exploit the therapeutic potential of T cells. To date, immunotherapy represents the most promising approach for patients refractory to conventional treatments. Immune responses against cancers rely mostly on T cells characterized by the expression of tumor-specific T cell receptors (TCRs) that allow them to specifically recognize and destroy malignant cells. Therapeutic strategies based on the transfer of natural tumor-specific T cells have been proven to be clinically successful with limited toxicity. Unfortunately, the clinical efficiency of this approach is hampered by the difficulty to obtain highly tumor-reactive and long-lived T cells for each patient.

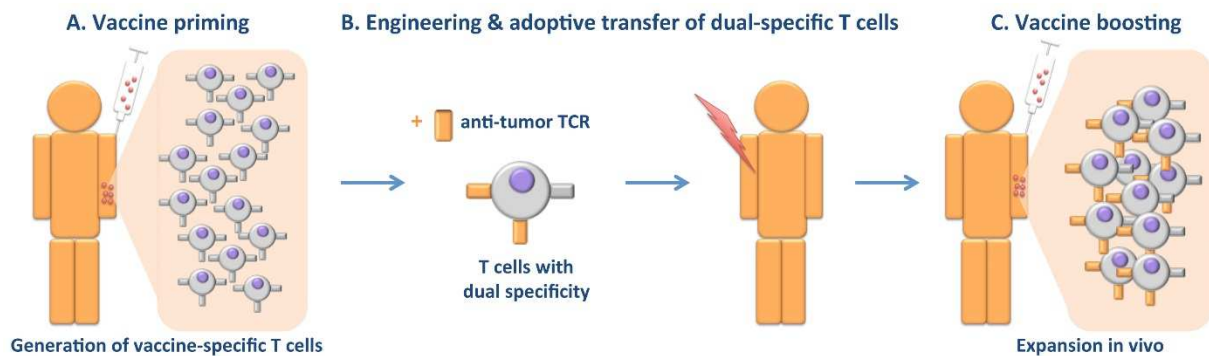
Objectives

T cell engineering has been developed, as an alternative strategy by which large numbers of tumor-specific T cells can be generated. Molecular modification of T cells relies on the gene transfer of optimized tumor-specific TCRs before their re-infusion into patients, and may increase the clinical efficacy. Moreover, this approach provides the opportunity to select for T cell subsets with greater potential to mediate efficient and long-lasting anti-tumor responses.

Immunization with live-virus vaccines mediates life-long protection associated with the development of persistent memory T cells over time. The present project, supported by the ISREC Foundation, aims at investigating the feasibility and advantage of engineered vaccine-specific T cells co-expressing optimized tumor-specific TCRs. Our hypothesis is that such dual-specific (anti-vaccine & anti-tumor) T cells could benefit from the ability of vaccine-induced memory to establish protective and long-lasting anti-tumor responses (Figure).

Results

We are currently addressing the feasibility of this approach by the in-depth characterization of *in vitro* engineered T cells with dual specificity (anti-vaccine & anti-tumor). We chose to engineer T cells directed against the yellow fever virus that spontaneously display a great potential for *in vivo* persistence. We optimized the isolation, culture and TCR gene-transfer procedures of yellow fever-specific T cells. We were able to generate dual-specific T cells expressing both TCRs and displaying dual (anti-tumor & anti-vaccine) reactivity. We also developed a panel of tools designed to characterize these T cells at the phenotype and function level, with a special emphasis on their anti-tumor capacity and survival potential.



Dual-specific T cells engineered for long-term immunotherapy of cancer: principle and process

(A) Vaccine-specific T cells are first generated *in vivo* through patient vaccination with a live-attenuated virus.

(B) Next, vaccine-specific T cells are engineered *ex vivo* to co-express an optimized anti-tumor TCR, and are infused back into the patient. **(C)** Vaccine boosts, which stimulate the expansion of dual-specific T cells *in vivo*, can be used to potentiate the therapeutic effect.

Perspectives

We are further planning to engineer T cells isolated from a cohort of yellow fever-vaccinated healthy donors. This will be done using a panel of affinity-optimized TCR to determine the optimal affinity/recognition of anti-tumor TCRs in a vaccine-specific context.

Finally, we will also investigate the therapeutic benefit of using engineered memory T cell subsets selected for their long-term persistence. Altogether, our project aims at implementing novel strategies to engineer anti-tumor T cells with optimal reactivity and long-lasting properties, and should provide rationale for the improvement of anti-cancer T cell-based therapies.

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FUNDS

FUND "FUNDAMENTAL RESEARCH"

Analysis of genomic instability in normal and cancer cells studied *ex vivo*

Collaboration between the EPFL and the Geneva University Hospital

This "allocated fund" from the Fondation de Bienfaisance Pictet and amounting to CHF 100'000.- per year was allocated in September 2014 for three years

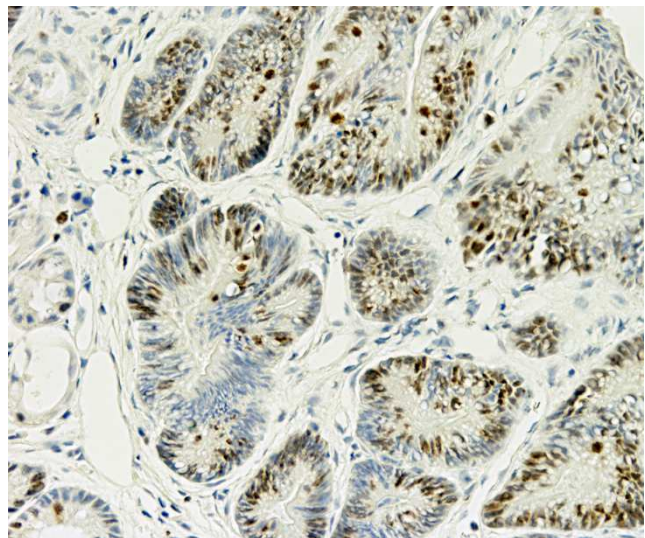
It was awarded to the research laboratories of **Prof. Joerg Huelsken** (EPFL/SV/ISREC)

Introduction

It is well established that one of the main features distinguishing cancer cells from normal cells is the presence of genomic instability. Such genomic instability is considered to be an important factor in driving cancer development, since the continuous generation of genomic alterations allows selection of cancer cell variants. This is the prerequisite for the evolution of ever more rapidly growing cells and can also explain the emergence of therapy-resistant cancer cells. There are several types of genomic instability. Chromosomal instability refers to changes in chromosome structure and number and can be found in nearly all cancers. Another type of genomic instability involves the acquisition of point mutations (single nucleotide substitutions). Some cancers are characterized by the presence of heritable mutations in DNA repair genes. These cancers acquire point mutations at a very high rate. However, they represent a small fraction of the cancer burden in humans. In the majority of human cancers, the DNA repair genes are not mutated. Accordingly, it has been argued by some that cancers do not show genomic instability at the level of point mutations. The proponents of this view argue that the mutations observed in human cancers simply reflect the high number of cell divisions that cancer cells have undergone. According to this view, highly replicating cells in healthy individuals would also have many point mutations in their genomes. However, since such cells have not been isolated in sufficient number, it is not possible to sequence their genome to establish their mutation burden.

Previous results

Our recent sequencing study of colon adenomas has demonstrated a mutation burden that correlates well with the size (and hence age) of the tumor. This result argues that colon adenomas, which are precancerous lesions, acquire point mutations at a higher rate than normal cells (about 200-fold higher). If this is true, several mechanisms can be envisioned to explain such a type of genomic instability. One mechanism could involve a difficulty in repairing DNA lesions in the context of single-stranded DNA. Normally, DNA is present in a double-stranded form which facilitates repair. However, problems with DNA replication in cancer lead to persistently separated DNA strands, and inefficient repair of single-stranded DNA would result in a higher mutation rate. Another mechanism that could lead to higher point mutation rates in cancers could involve the production of reactive oxygen species (ROS), which can lead to increased levels of DNA damage.



Cell division in a colon cancer specimen

Research aims

We now propose to address two important questions that are central to our understanding of human cancer development and emergence of resistance to therapy:

1. Do cancers have an increased rate of acquisition of point mutations? And, if so,
2. what are the mechanisms leading to such an increased rate of acquisition of point mutations?

To address these questions, we propose two specific aims:

1. To determine the mutation load in normal and cancer colon cells. The colon is one of the very few tissues in which normal cells and cancer cells have equal cell division rates, allowing us to establish whether mutation rates are the same or different in the two types of cells.
2. To examine the mechanisms leading to acquisition of point mutations in normal and cancer cells, with a focus on DNA replication stress and ROS production.

ORGANISATION

Founded on June 18th 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 promote the transfer of knowledge and collaboration between fundamental 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:

THE FOUNDATION COUNCIL

The Foundation Council is the highest managing authority of the Foundation. It allocates resources, appoints its members as well as those of the Scientific Board, of the Management and of the Financial Auditors. Moreover, it approves the annual budget and the Foundation accounts.

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Director, Clinic and Policlinic for Medical Oncology, Inselspital - Bern University Hospital

MANAGEMENT

With the help of Scientific Board, the Management selects the research projects to be supported and addresses its opinion to the Foundation Council. It develops and proposes a strategy of fundraising and assumes the tasks allotted by the regulations of the Foundation.

Prof. Francis-Luc Perret
Director

THE FINANCIAL AUDITORS

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 SA**, Swiss Fiduciary and Audit Company recognized by the Swiss Institute of Certified Accountants and Tax Consultants.

FINANCES

RESOURCES

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 31st 2014, the fortune of the foundation amounted to CHF 53 million.

Total subsidies remitted in 2014	CHF	2'453'000
in support of scientific and academic training	CHF	353'000
Grant "Cancer and immunology"	CHF	40'000
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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
12 Grants "International Summer Research Program"	CHF	33'000
in support of translational cancer research	CHF	2'100'000
ISREC Chair "Translational oncology"	CHF	500'000
ISREC Chair "Translational oncology"	CHF	500'000
ISREC Chair "Translational oncology"	CHF	500'000
Fund "Translational research - glioblastoma"		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"		balance paid in 2013
Fund "Fundamental research"	CHF	100'000
Total gifts, donations, legacies, external grants received in 2014	CHF	5'469'761
58 spontaneous gifts from private individuals	CHF	174'162
16 gifts from companies, associations, foundations	CHF	231'500
8 gifts for allocated grants / funds	CHF	4'359'458
84 gifts in memory of deceased people	CHF	38'768
35 legacies, successions	CHF	665'873
Capital of the Foundation (Free funds)	CHF	38'167'717
Reserved capital (Limited allocation funds)	CHF	8'181'908
Grants	CHF	420'000
Funds	CHF	1'261'908
ISREC chairs	CHF	6'500'000
Reserved capital AGORA – Cancer Center	CHF	2'777'091

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MAKE A DONATION

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 funding 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.

THANK YOU FOR YOUR SUPPORT

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A deduction of up to 20% of net income is possible, as long as the payment amounts to a minimum of CHF 100.-.

> Taxes at the cantonal level

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ISREC FOUNDATION TAXATION

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

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Since 1964, numerous donors have supported our cause and contributed to the progress of cancer research through their gifts, subsidies or legacies.

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

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

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