FONDATION
MEDIC

Consortium "Tumor-Host Interaction" supported by the MEDIC Foundation

Annual Report 2011

1. Introduction

The theme 'Tumor-host interaction' chosen for the consortium, created in 2006 around the project groups funded by grants from the MEDIC Foundation, remains of primary interest. Of the 11 projects presently supported by MEDIC, 9 were renewed in 2011 based upon review of a full new grant application (some conditional following critical reviews) and most of them developed very favorably. Once again the increasing interaction between the different groups in the consortium has been a highlight, several of them active in studies they might not have taken on had it not been for partnerships developed within the MEDIC consortium. This is partly (but not only) due to a strong role played by the group of expert bio-informaticians in the management of the high throughput data many of the groups generate. The external Scientific Advisory Board, which has been instrumental in the decision making process that culminated in awarding the first MEDIC prize, has been reinforced and consolidated. Annual scientific and financial reports are reviewed. The consortium members continue to meet annually in Lausanne and present in symposium format the progress made and the new projects that will be or have been submitted for funding. The program of the 2011 meeting, which was organized somewhat earlier in the year (October) to avoid the potential problems with traveling in the winter, is presented in table 1.

Table 1 Programme of the MEDIC day 2011

A. Mariotti	Function of MFG-E8/lactadherin in cancer progression
C. Ruegg	Heterotypic interactions in the tumor microenvironment: contribution to tumor metastasis
V. Piguet	Global analysis of transcription reveals BCSC-1 as a melanoma tumor suppressor that downregulates MITF
G. Ghanem	New treatments, new markers in melanoma
L. Julien	Proangiogenic programming of $CD11b^+$ myelomonocytes in breast cancer by PlGF during hematopoietic progenitors differentiation
M. Delorenzi	Analysis of Molecular Profiles and Gene Expression in clinical samples of colon cancer
C. Sotiriou	Update on the results of the breast cancer stroma project and introduction to our new research program on breast cancer molecular heterogeneity
D. Picard	Mechanistic studies on signalling crosstalk by the estrogen receptor alpha suggest new therapeutic schemes for breast cancer
T. Petrova	Transcriptional control of colon cancer
P. Martiat	The immuno-blood and marrow environment in acute leukemia: a study of natural and induced Tregs and a transcriptomic analysis of infiltrating CD3
P.Romero	Role of microRNA in CD8 T cell functions
I.Stamenkovic	Mechanisms that govern energy regulation in cancer

The annual reports and the annual meeting presentations provide the SAB the tools to critically follow the progress made in the studies. It was decided to proceed to the creation of a web-site, to facilitate the communication between consortium members and improve visibility of the activities supported by MEDIC.

Productive collaborations continue to develop, justifying the decision to choose for this approach. The chosen theme "tumor-host interaction" continues to be timely and allows both a common focus in the research projects as well as significant latitude in the development of the individual research lines. One group was terminated, due to a change in direction of the research activities in the Oncology Center in Lausanne. Part of the group resurfaced in Fribourg and allowed the consortium to expand further into the cancer research activities in the region.

2. Research groups, themes and received support

Table 2 lists the research projects that are supported by the MEDIC Foundation, the project title and the total amount of annual support received.

Table 2 List of projects funded by the MEDIC foundation

C.Ruegg	Role of CYR61 in tumor progression and metastasis	CHF	260'000.-
A.Mariotti	Signaling function of Lactadherin in mammary gland carcinomas	CHF	112’120,-
D.Picard	Molecular and pharmacological investigation of the factors contributing to tamoxifen resistance of ERa-positive breast cancers	CHF	147’340.-
M.Delorenzi	Tumor expression profiling. In silico modeling of tumor stroma	CHF	238'400.-.-
V.Piguet	Molecular pathways in melanoma progression	CHF	125’000,-
T.Petrova	Analysis of PROX1 role in colon and small cell lung cancers	CHF	176'000.-
I.Stamenkovic	Tumor-host interactions in cancer progression and metastasis	CHF	83.000.-
P.Romero	Role of microRNAs in CD8 T cell function	CHF	114’012.-
C.Sotiriou	Tumor-host interaction in breast cancer	€	360'000.-
G.Ghanem	Regulation of Ras/Raf/MEK/ERK Map kinase pathway and melanoma progression	€	153'000.-
Ph.Martiat	Leukemia-host interaction	€	226'864.-

It is relevant here to note that the total volume of MEDIC supported research conducted in Lausanne has grown and in 2011 6 groups profited from MEDIC support. A new Lausanne group has been accepted following positive external review and will be financed in 2012 (L. de Leval). With the expansive growth of cancer research in the Lausanne academic

community this does not come as a surprise. The second biggest site is Institut Jules Bordet with 3 project groups. Geneva participated with 2 groups, one of which has been terminated end 2011 (Principal Investigator moved elsewhere).

3. Research programme

Three clusters of activities can be distinguished: general aspects of tumor biology, the pathobiology of breast cancer, pathobiology of colon cancer and cancer immunotherapy.

3.1 General aspects of tumor biology

This heading puts together research lines which address questions concerning the development and behaviour of cancer cells more in general and not necessarily limited to an organ or organ system. Two research lines fall into this category: the complex interactions between a variety of cells and molecules that make up the host response to growing tumor cells and basic aspects of cell function that are disrupted in cancer cells.

1. **Heterotypic interactions is the host response to tumor cell growth**
   Principal Investigator: Curzio Ruegg

The main focus of the laboratory is the study of the tumor microenvironment (tumor-host interaction). In recent years we have learned that the tumor microenvironment plays an important role promoting tumor progression. Tumor angiogenesis and bone marrow-derived and inflammatory cells recruited at tumor sites have emerged as critical determinant of tumor progression. Our understanding of the functional relationship between the tumor microenvironment and tumor cells is still limited. This is becoming particularly relevant in view of the potential targeting of stromal event to inhibit tumor progression. The main questions addressed in the laboratory include:

-How do cells of the microenvironment, in particular inflammatory cells, promote tumor growth and metastasis, and how do therapeutic interventions modify the tumor microenvironment and how do these modifications impact tumor behavior?

- How does the cross-talk between tumor cells and the microenvironment evolve during progression to metastasis ?

During the elapsed year we have progressed in the characterization of two molecules we have previously identified to be involved in tumor-host interaction.

MAGI1. Regular use of non-steroidal anti-inflammatory drugs or selective COX-2 inhibitors (COXIBs) reduces the risk of cancer development and progression, in particular of the colon, but the mechanisms involved are not fully understood. We identified MAGUK with Inverted domain structure-1 (MAGI1), a scaffolding protein implicated in the stabilization of adherens junctions, as a gene upregulated by COXIB in colorectal cancer (CRC) cells and acting as tumor suppressor. Overexpression of MAGI1 in CRC cell lines SW480 and HCT116 stabilized E-cadherin and β-catenin localization at cell-cell junctions; increased cell adhesion and suppressed Wnt signaling, anchorage-independent growth, migration and invasion in vitro. Conversely, MAGI1 silencing decreased E-cadherin and β-catenin localization at cell-cell junctions

and enhanced Wnt signaling, anchorage-independent growth, migration and invasion in vitro. MAGI1 overexpression suppressed SW480 and HCT116 tumor growth and attenauted metastasis in various experimental models. These results identify MAG1 as a COXIB-induced inhibitor of the Wnt/β-catenin signaling pathway, with tumor-suppressive and anti-metastatic activity in experimental colon cancer. R1CYR61 and R1CYR61R1T2 mice were generated.

CYR61. We have previously reported that CYR61 promotes lug metastasis of tumors growing in preirradiated beads, as it occurs during relapses after radiotherapy. The mechanisms involved has remained elusive. In vitro experiments suggested a possible role of CRY61 in promoting EMT. In order to gain an unbiased insight into CYR61 effects on tumor progression we opted for a transgenic approach by using the Rip1Tag2 (R1T2) model of multistep tumor progression. Results obtained using these mice demonstrate that CYR61 promotes tumor growth and invasion but not (full) EMT or metastasis. No enhanced tumor angiogenesis was observed in these mice. In a coculture model of colorectal cancer cells and fibroblasts, fibroblasts induce an elongated and motile phenotype in CRC cells, which correlates with elevated levels of CYR61 and expression of EMT genes. Taken together these results indicate that CYR61 promotes tumor growth and invasion, but is not sufficient to cause metastasis or full EMT.

Publications

Laurent J, Touvrey C, Botta F, Kuonen F, Ruegg C.Emerging paradigms and questions on pro-angiogenic bone marrow-derived myelomonocytic cells. Int J Dev Biol. 2011;55:527-34.

Zaric J, Joseph JM, Tercier S, Sengstag T, Ponsonnet L, Delorenzi M, Rüegg C. Identification of MAGI1 as a tumor-suppressor protein induced by cyclooxygenase-2 inhibitors in colorectal cancer cells. Oncogene. 2011;31:48-59

Rüegg C, Monnier Y, Kuonen F, Imaizumi N. Radiation-induced modifications of the tumor microenvironment promote metastasis. Bull Cancer. 2011;98:47-57

Kuonen F, Secondini C, Rüegg C. Molecular pathways: emerging pathways mediating growth, invasion, and metastasis of tumors progressing in an irradiated microenvironment. Clin Cancer Res. 2012;18:5196-202

Kuonen F, Laurent J, Secondini C, Lorusso G, Stehle JC, Rausch T, Faes-Van't Hull E, Bieler G, Alghisi GC, Schwendener R, Andrejevic-Blant S, Mirimanoff RO, Rüegg C. Inhibition of the Kit ligand/c-Kit axis attenuates metastasis in a mouse model mimicking local breast cancer relapse after radiotherapy. Clin Cancer Res. 2012;18:4365-74.

Lorusso G, Rüegg C. New insights into the mechanisms of organ-specific breast cancer metastasis. Semin Cancer Biol. 2012;22:226-33 Sleeman JP, Christofori G, Fodde R, Collard JG, Berx G, Decraene C, Rüegg C. Concepts of metastasis in flux: the stromal progression model. Semin Cancer Biol. 2012;22:174-86

2. Cell cycle control functions of securin and separase

Principal Investigator: Ivan Stamenkovic

Regulation of cell division is a central issue in cancer research as one of the hallmarks of cancer is uncontrolled cell growth. Part of the problem is that too many cells divide too fast, resulting in too many cells. Part of the problem is that segregation of chromosomes over the daughter cells is not well regulated, leading to chromosomal imbalances. The Stamenkovic laboratory has studied proteins involved in these processes (securin and separase) of which new functions have been identified that suggest that they also play a role in secretory processes.

Securin and separase play a key role in sister chromatid separation during anaphase. However, a growing body of evidence suggests that in addition to regulating chromosome segregation, securin and separase display functions implicated in membrane traffic in Caenorhabditis elegans and Drosophila. We have shown that in mammalian cells both securin and separase associate with membranes and that depletion of either protein causes robust swelling of the trans-Golgi network (TGN) along with the appearance of large endocytic vesicles in the perinuclear region. These changes are accompanied by diminished constitutive protein secretion as well as impaired receptor recycling and degradation. Unexpectedly, cells depleted of securin or separase display defective acidification of early endosomes and increased membrane recruitment of vacuolar (V-) ATPase complexes, mimicking the effect of the specific V-ATPase inhibitor Bafilomycin A1. Taken together, our findings identify a new functional role of securin and separase in the modulation of membrane traffic and protein secretion that implicates regulation of V-ATPase assembly and function.

Publications

Bacac M, Fusco C, Planche A, Santodomingo J, Demaurex N, Leemann-Zakaryan R, Provero P, Stamenkovic I. Securin and separase modulate membrane traffic by affecting endosomal acidification. Traffic. 2011;12:615-26.

3.2 The pathobiology of breast cancer

Several groups in the consortium work on breast cancer, which is the most frequently encountered type of cancer in women since 1 out of 9 will develop breast cancer and unfortunately one third of these will subsequently die from this disease. The currently used factors for predicting survival and response to treatment do not sufficiently explain why in some patients the tumors progress and in others do not or why some women respond well to therapy whereas in others the tumors continue to grow. During the last years, several prognostic predictors have been developed in breast cancer using gene expression profiling technologies. Although these predictors outperform the currently used clinico-pathologic factors, they remain suboptimal. This means that in order to get a better picture of breast cancer biology, additional elements need to be considered, such as: 1) the tumor microenvironment and 2) the disseminated and circulating tumor epithelial cells. These key elements constitute the main research axes of this group of projects. Three research projects in the consortium focus on aspects of breast cancer.

1. **Genetic heterogeneity of breast cancer**
   Principal Investigator Christos Sotiriou

In order to get a better picture of breast cancer biology, in this project it was decided that 1) the tumor microenvironment and 2) the disseminated and circulating tumor epithelial cells needed to be more carefully studied. The tumor microenvironment consists of elements that are contributed to the tumor by the host (including vessels, mesenchymal stromal cells and inflammatory cells) and signalling molecules which play a role in the communication between cancer cells and the host response. Circulating tumor cells have been found to constitute an integral part of the biology of cancer. Their significance is insufficiently clear, although at least a fraction of these circulating cells must be responsible for cancer metastasis.

There is growing evidence that interaction between stromal and tumor cells is pivotal in breast cancer progression and response to therapy. Based on earlier research suggesting that during breast cancer progression, striking changes occur in CD10(+) stromal cells, we aimed to better characterize this cell population and its clinical relevance. We developed a CD10(+) stroma gene expression signature (using HG U133 Plus 2.0) on the basis of the comparison of CD10 cells isolated from tumoral (n = 28) and normal (n = 3) breast tissue. We further characterized the CD10(+) cells by coculture experiments of representative breast cancer cell lines with the different CD10(+) stromal cell types (fibroblasts, myoepithelial, and mesenchymal stem cells). We then evaluated its clinical relevance in terms of in situ to invasive progression, invasive breast cancer prognosis, and prediction of efficacy of chemotherapy using publicly available data sets.This 12-gene CD10(+) stroma signature includes, among others, genes involved in matrix remodeling (MMP11, MMP13, and COL10A1) and genes related to osteoblast differentiation (periostin). The coculture experiments showed that all 3 CD10(+) cell types contribute to the CD10(+) stroma signature, although mesenchymal stem cells have the highest CD10(+) stroma signature score. Of interest, this signature showed an important role in differentiating in situ from invasive breast cancer, in prognosis of the HER2(+) subpopulation of breast cancer only, and potentially in nonresponse to chemotherapy for those patients. Our results

highlight the importance of CD10(+) cells in breast cancer prognosis and efficacy of chemotherapy, particularly within the HER2(+) breast cancer disease.

We furthermore studied aberrant microRNA (miRNA) expression, as a complementary tool to improve our understanding of breast cancer (BC) biology and to assess whether miRNA expression could predict clinical outcome of BC patients. Global miRNA expression profiling using microarray technology was conducted in systemically untreated BC patients who had corresponding mRNA expression profiles available. Results were further confirmed using qRT-PCR in an independent dataset of 89 ER-positive BC patients homogeneously treated with tamoxifen only. MiR-210 functional analyses were performed in MCF7 and MDA-MB-231 BC cell lines using lentiviral transduction. Estrogen receptor (ER) status, tumor grade and our previously developed gene expression grade index (GGI) were associated with distinct miRNA profiles. Several miRNAs were found to be clinically relevant, including miR-210, its expression being associated with tumor proliferation and differentiation. Furthermore, miR-210 was associated with poor clinical outcome in ER-positive, tamoxifen-treated BC patients. Interestingly, the prognostic performance of miR-210 was similar to several reported multi-gene signatures, highlighting its important role in BC differentiation and tumor progression. Functional analyses in BC cell lines revealed that miR-210 is involved in cell proliferation, migration and invasion. This integrated analysis combining miRNA and mRNA expression demonstrates that miRNA expression provides additional biological information beyond mRNA expression. Expression of miR-210 is linked to tumor proliferation and appears to be a strong potential biomarker of clinical outcome in BC.

Publications

Fumagalli D, Michiels S, Sotiriou C. CD44+ CD24-/low phenotype and resistance to trastuzumab in HER2-positive breast cancer cell lines. Pharmacogenomics. 2011;12:12-3.

Desmedt C, Michiels S, Haibe-Kains B, Loi S, Sotiriou C. Time to move forward from "first-generation" prognostic gene signatures in early breast cancer. Breast Cancer Res Treat. 2011 ;128:643-5.

Criscitiello C, Azim HA Jr, Schouten PC, Linn SC, Sotiriou C.Understanding the biology of triple-negative breast cancer. Ann Oncol. 2012;Suppl 6:vi13-vi18.

Desmedt C, Voet T, Sotiriou C, Campbell PJ.Next-generation sequencing in breast cancer: first take home messages. Curr Opin Oncol. 2012;24:597-604.

Ignatiadis M, Sotiriou C, Pantel K.Minimal residual disease and circulating tumor cells in breast cancer: open questions for research. Recent Results Cancer Res. 2012;195:3-9.

Ignatiadis M, Singhal SK, Desmedt C, Haibe-Kains B, Criscitiello C, Andre F, Loi S, Piccart M, Michiels S, Sotiriou C. Gene modules and response to neoadjuvant chemotherapy in breast cancer subtypes: a pooled analysis. J Clin Oncol. 2012;30:1996-2004.

Desmedt C, Majjaj S, Kheddoumi N, Singhal SK, Haibe-Kains B, El Ouriaghli F, Chaboteaux C, Michiels S, Lallemand F, Journe F, Duvillier H, Loi S, Quackenbush J, Dekoninck S, Blanpain C, Lagneaux L, Houhou N, Delorenzi M, Larsimont D, Piccart M, Sotiriou C. Characterization and clinical evaluation of CD10+ stroma cells in the breast cancer microenvironment. Clin Cancer Res. 2012;18:1004-14.

Metzger-Filho O, Michiels S, Bertucci F, Catteau A, Salgado R, Galant C, Fumagalli D, Singhal SK, Desmedt C, Ignatiadis M, Haussy S, Finetti P, Birnbaum D, Saini KS, Berlière M, Veys I, de Azambuja E, Bozovic I, Peyro-Saint-Paul H, Larsimont D, Piccart M, Sotiriou C. Genomic grade adds prognostic value in invasive lobular carcinoma. Ann Oncol. 2012. [Epub ahead of print]

Fumagalli D, Andre F, Piccart-Gebhart MJ, Sotiriou C, Desmedt C.Molecular biology in breast cancer: Should molecular classifiers be assessed by conventional tools or by gene expression arrays? Crit Rev Oncol Hematol. 2012. [Epub ahead of print]

2. Mechanisms of functioning of the estrogen receptor

Principal Investigator Didier Picard

Estrogen receptor (ER) plays an important role in breast cancer, both in terms of cancer biology and as predictor of response to therapy: ER positive tumors are likely to respond to anti-estrogen drugs (notably tamoxifen). Estrogen receptor positive breast cancers tend to develop resistance for tamoxifen, however. The Picard laboratory studies the molecular biology of the estrogen receptor against this background. Mechanisms of resistance are explored as well as possibilities to overcome this resistance.

The project comprised of several sub-projects:

- Alternate Era-mediated responses:

We have pursued our efforts to understand the molecular biology and the pathological relevance of the activation of ERα by alternate pathways, notably cAMP. To map all ERα binding sites in the genome when ERα is activated by cAMP (signalling crosstalk) we are collaborating with Wilbert Zwart (NKI Amsterdam) and Jason Carroll (Cancer Research UK, Cambridge). We have found that the cAMP-induced ERα binding sites (ERBS) are largely a subset of those induced by estradiol (E2). We then correlated ERBS with the genes whose expression is regulated by cAMP in an ERα-dependent fashion. This allowed us to come up with a list of genes that are particularly worth looking at in more detail. For these, preliminary validation experiments confirmed both the ERBS and the regulation of gene expression. Another interesting finding comes from examining the vicinity of the ERBS binding sequences. These appear to be enriched for ATF/CREB binding sites. We are now in the process of examining the mechanistic relevance of that association. We have no doubt that this global study will turn out data that are relevant to breast cancer as well. For example, we have found that genes that have an ERBS associated with them and are upregulated by cAMP constitute a signature associated with poor outcome.

- The arginine methylase CARM1 as cAMP-regulated ERα activator:

We have followed up on our discovery that CARM1 mediates the activation of ERα by cAMP and thereby contributes to tamoxifen resistance in breast cancer. We developed an antiserum that is specific for the PKA-posphorylated CARM1 and now hope to use it to characterize a panel of breast tumor biopsies in collaboration with

Christos Sotirious's lab. Furthermore, we are about to do a comparative Chip-seq experiment with this antiserum to determine whether the PKA-phosphorylated CARM1 colocalizes with ERα at a genome-wide level. We are also in the process of characterizing the interaction of CARM1 and ERα ιn more detail and to determine whether PAK1, often activated in breast cancer, could be an alternative activator of CARM1 and thus ERα

- Role of Hsp90 for activation of ERα by cAMP and tamoxifen resistance:

We discovered that Hsp90 is required for activation of ERα by cAMP. This is further corroborated by the finding that the histone deacetylase 6 (HDAC6), a known activator of Hsp90, is most likely required as well. Based upon these findings, we have speculated that tamoxifen sensitivity might be restored by treating cells with Hsp90 or HDAC6 inhibitors. We have begun experiments with geldanamycin as a specific Hsp90 inhibitor and with tubastatin that has been reported to be HDAC6-selective. Preliminary experiments are encouraging but more are required to answer the initial question.

- miRNAs regulating ERα expression:

While we have confrmed repeatedly that miR-22 represses ERα expression and estrogen responses in breast cancer cells, we have not been able to confirm that for other miRNAs that we have been investigating for some time. In the meantime, we have received a conditional mouse KO for the miR-22 gene. We expect the first results with this mutant in the first part of 2012.

- Yeast as a screening tool for novel ERα regulators:

As mentioned before, several candidates came out of the screen. While they have all been validated in yeast, validating and characterizing them in mammalian cells has proven more difficult than originally anticipated. We are still studying VPS11 and VPS16, two proteins that might link ERα function to membrane traffic.

- RNAi screen in mammalian cells:

The genome wide screens to identify the factors required for ERα and glucocorticoid receptor signalling were done in November 2010 by a graduate student. Following his departure from the lab a month later, the bioinformatic analysis of this part of this highly complex data set took a long time. That part is essentially done now and we can begin to use the data. We have already selected some candidates for validation and further characterization.

Publications

Lappano R, Recchia AG, De Francesco EM, Angelone T, Cerra MC, Picard D, Maggiolini M. The cholesterol metabolite 25-hydroxycholesterol activates estrogen receptor α-mediated signaling in cancer cells and in cardiomyocytes. PLoS One. 2011;6:e16631.

Echeverría PC, Bernthaler A, Dupuis P, Mayer B, Picard D. An interaction network predicted from public data as a discovery tool: application to the Hsp90 molecular chaperone machine. PLoS One. 2011;6:e26044.

Echeverría PC, Forafonov F, Pandey DP, Mühlebach G, Picard D Detection of changes in gene regulatory patterns, elicited by perturbations of the Hsp90 molecular chaperone complex, by visualizing multiple experiments with an animation. BioData Min. 2011;4:15.

Ge X, Rameix-Welti MA, Gault E, Chase G, dos Santos Afonso E, Picard D, Schwemmle M, Naffakh N.Influenza virus infection induces the nuclear relocalization of the Hsp90 co-chaperone p23 and inhibits the glucocorticoid receptor response.PLoS

3. New prognostic factors in breast cancer: lactadherin

Principal Investigator Agnese Mariotti

In the sera of patients with disseminated breast cancer the secreted glycoprotein MFGE8/lactadherin is present at high levels. In this project we have found that MFGE8/lactadherin increases tumorigenic potential of breast cancer cells and confers increased growth potential to normal breast epithelial cells. Our data indicate that this protein cooperates with oncogenes to promote cell transformation and increases malignant behaviour of cancer cells and favours tumour progression.

MFGE8/lactadherin is a secreted glycoprotein that is present at high levels in the sera of patients with disseminated breast cancer. We have recently demonstrated that mFGE8/lactadherin enhances the tumorigenic potential of mammary carcinoma cells and promotes in vitro growth of non-tumorigenic mammary epithelial cells. Our data indicate that this protein has a dual function: it can cooperate with oncogenes and promote cell transformation and it can increase malignancy of carcinoma cells and favour further tumor growth. We have also shown that in breast carcinomas high levels of lactadherin are associated with lack of estrogen receptor expression, and they can be found in tumors expressing ErbB2 but not in those bearing ErbB2 amplification. Our data, together with those published by another group, suggest that lactadherin function varies in different breast carcinoma subtypes. In addition, when analysing genes whose expression is correlated with lactadherin in breast carcinoma we have found that Sox10 has the highest positive correlation, suggesting a possible functional link between the two proteins and a still unsuspected role for Sox10 in breast cancer development. The project aims to clarify lactadherin function in different breast carcinoma subtypes and to gain insight in the signalling pathways downstream of it that may contribute to breast carcinoma development. We also propose to analyse Sox 10 expression in breast carcinoma by both bioinformatics and immunohistochemistry and to investigate its function in breast carcinoma cells. The research proposed here will allow us to identify those breast carcinomas whose progression is promoted by lactadherin and that thus may respond to therapeutic inhibition of lactadherin function, and to discover if Sox 10 plays a role in breast cancer.

Publications

Carrascosa C, Obula RG, Missiaglia E, Lehr HA, Delorenzi M, Frattini M, Rüegg C, Mariotti A. MFG-E8/lactadherin regulates cyclins D1/D3 expression and enhances the tumorigenic potential of mammary epithelial cells.Oncogene. 2012;31:1521-32.

3.3 The pathobiology of colon cancer

Colon cancer is the second most frequent cancer type in the western world in females and males. In spite of the fact that it is one of the most widely studied types of cancer and that the concept of stepwise progression of molecular events has been developed based on colorectal carcinogenesis many questions around this tumor type remain unsolved and overall about 50% of the patients with this disease cannot be cured. It is therefore not surprising that in the MEDIC consortium a significant effort is directed towards contributing answers to these questions. Two research lines address colorectal cancer.

1. Molecular heterogeneity of colorectal cancer

Principal Investigator Mauro Delorenzi

In this project the molecular heterogeneity of colorectal cancer is studied in a large series of cases, with detailed clinical follow-up. The basic question asked in this project is why some colorectal carcinomas do not recur after initial treatment but others recur, metastasize and finally kill the patient. Better understanding of this heterogeneity in molecular terms could lead to new diagnostic tools (determining who needs further treatment after initial surgery and who is likely to respond to therapy) and the development of new drugs effective in colorectal cancer.

In colorectal cancer, our efforts have focused on the PETACC-3 multicenter randomized phase III study conducted within the Pan-European trial Adjuvant Colon Cancer (PETACC) network. The trial was designed to study whether addition of irinotecan to infusional 5-FU/FA would improve disease free survival (DFS) when compared to 5-FU/FA alone as adjuvant treatment in stage II and III colon cancer patients. The tissue specimen repository in Lausanne allowed immunohistochemical marker testing in Genova and in Lausanne and gene expression profiling, gene copy number assessment and analysis of genome aberrations among others in Leuven. Data management and statistical analysis are performed by the statistic unit of the Swiss Group of Clinical Cancer Research (SAKK) in Bern, and our group in Lausanne. We examined in this data set the correlation of BRAF and KRAS mutations, microsatellite instability (MSI), chromosome 18q loss of heterozygosity (18qLOH), and SMAD4 expression with survival in terms of relapse-free survival (RFS) and overall survival (OS). MSI-high status and SMAD4 focal loss of expression were identified as independant prognostic factors with better RFS and OS for MSI-H status and worse RFS and OS for SMAD4 loss. 18qLOH did not have any prognostic value in RFS or OS. Recursive partitioning identified refinements of TNM into new clinically interesting prognostic subgroups. Notably, T3N1 tumors with MSI-high status and retained SMAD4 expression had outcomes similar to stage II disease.
We furthermore developed a BRAF-mutant gene expression signature for colon cancer (CC) and studied its prognostic implications. To this end we used the expression profiles of BRAF mutant and non-BRAF, non-KRAS mutant cancers (double wild type) and constructed a gene expression-based classifier for detecting BRAF mutant samples with high sensitivity. The classifier was validated in independant data sets, and survival rates were compared between classifier positive and negative tumors. A 64 gene-based classifier was developed with 96% sensitivity and 86% specificity for detecting BRAF mutant tumors in PETACC-3 and independant samples. A

subpopulation of BRAF wild-type patients (30% of KRAS mutants, 13% of double wild type) showed a gene-expression pattern and had poor overall survival and survival after relapse, similar to those observed in BRAF-mutant patients. Thus they form a distinct prognostic subgroup within their mutation class. The characteristic pattern of gene-expression is associated with and accurately predicts BRAF mutation status and, in addition, identifies a population of BRAF mutated-like KRAS mutants and double wild-type patients with similarly poor prognosis. These results may guide therapeutic strategies for this patient segment and may help in population stratification for clinical trials.
We are presently investigating in further detail molecular heterigeneity of colorectal cancer.

Publications

Tejpar S, Saridaki Z, Delorenzi M, Bosman F, Roth AD. Microsatellite instability, prognosis and drug sensitivity of stage II and III colorectal cancer: more complexity to the puzzle. J Natl Cancer Inst. 2011;103:841-4

Rossi S, Di Narzo AF, Mestdagh P, Jacobs B, Bosman FT, Gustavsson B, Majoie B, Roth A, Vandesompele J, Rigoutsos I, Delorenzi M, Tejpar S.microRNAs in colon cancer: a roadmap for discovery. FEBS Lett. 2012;586:3000-7.

Roth AD, Delorenzi M, Tejpar S, Yan P, Klingbiel D, Fiocca R, d'Ario G, Cisar L, Labianca R, Cunningham D, Nordlinger B, Bosman F, Van Cutsem E. Integrated Analysis of Molecular and Clinical Prognostic Factors in Stage II/III Colon Cancer.
J Natl Cancer Inst. 2012 7;104:1635-46.

Tian S, Roepman P, Popovici V, Michaut M, Majewski I, Salazar R, Santos C, Rosenberg R, Nitsche U, Mesker WE, Bruin S, Tejpar S, Delorenzi M, Bernards R, Simon I. A robust genomic signature for the detection of colorectal cancer patients with microsatellite instability phenotype and high mutation frequency. J Pathol. 2012. doi: 10.1002/path.4092.

2. The role of Prox1 in colon cancer progression and metastasis

Principal Investigator Tatiana Petrova

In this project one particular molecular mechanism in colorectal cancer is studied. This consists of PROX1, a molecule that has been shown to be involved in intestinal adenoma development in mouse models. The experiments conducted have shown that PROX1 is involved in the interaction between the cancer cells and the host stromal cells. Furthermore, PROX1 is closely associated with the signaling pathway involved in regulation of cell differentiation in intestinal mucosa (the Wnt pathway) and also in transformation of intestinal epithelial cells into cancer cells. Present data suggest that PROX1 is involved in progression to later stages (e.g.metastasis) rather than in the initial stages of colorectal cancer development.

The main goal of our project is to investigate the contribution of transcription factors to the colon and lung tumorigenesis.
1. To better understand the mechanisms of PROX1 action in CRC, we have identified

PROX1 interacting proteins using shotgun proteomics approach and in situ proximity ligation assay. We found that PROX1 is a part of TCF/b-catenin transcriptional complex in cultured colon cancer cells, mouse intestinal epithelial cells with activated Wnt signaling and human colon adenocarcinomas. To understand the mechanism of PROX1 action, we have interrogated the genome of colon cancer cells for PROX1, TCF4 (TCF7L2) and b -catenin binding sites and we show that TCF4, b -catenin and PROX1 simultaneously bind to a subset of genomic enhancers, on which PROX1 acts as a transcriptional repressor. These results suggest that PROX1 is a colon-cancer specific modifier of TCF/ b -catenin signal transduction pathway. We propose that this is one of the mechanisms by which sustained Wnt signaling observed in the majority of colon cancers transforms an initially normal intestinal progenitor program into a cancer-specific output, which will later contribute to unrestricted tumor growth, invasion and dissemination (Ivanov, Cheng et a1., manuscript under review).
2. We have studied whether PROX1 contributes to later stages of CRC, such as tumor metastasis (Ragusa et al., manuscript in preparation). Using a panel of 160 primary CRC tumors, we found that PROX1 expression is restricted to microsatellite stable cancer subtype, which has worse prognosis in comparison to microsatellite instable CRC (in collaboration with Dr. G. Marra, University of Zurich, and Dr. F. Bosman, CHUV). Furthermore, PROX1 expression was observed in metastatic CRC lesions in lymph nodes and liver (in collaboration with Dr. H. Bouzourene, IUP, CHUV). Suppression of PROX1 in PROX1+ SW620 cells, derived from the metastatic lymph node lesion, strongly reduced development of metastases in an orthotopic model of CRC. In line with these results, PROX1 overexpression in PROXl-negative DLDI CRC cells significantly enhanced the development of metastases. Surprisingly, growth of primary tumor was not affected in either cell line, suggesting that PROX1 has distinct roles in adenomas vs. carcinomas.
3. To establish whether targeting PROX1 pathway is a potentially viable clinical approach, we have studied the effects of PROX1 suppression after the establishment of primary tumor and metastases. While control mice developed rampant metastatic lesions, suppression of PROX1 arrested growth of metastases. Taken together, these results suggest that PROX1 has a role beyond the regulation of the transition from benign adenoma to carcinoma in situ identified previously (Petrova et a1., 2008) and that a PROXl-regulated transcriptional network contributes to outgrowth of micrometastases, which is currently one of the least studied and most deadly aspects of tumorigenesis. Importantly, in addition to constitutive activation of Wnt pathway, SW480, SW620 and DLDI cells used in our study are also mutant for KRAS. Mutations of KRAS identify a group of patients poorly responsive to anti-EGFR therapy currently used for the treatment of metastatic CRC. Thus, patients with metastatic microsatellite stable/PROX1high/KRAS mutant tumors, for whom only limited treatment options are available, may potentially benefit if suitable inhibitors of PROX1 activity or expression in CRC cells are identified.

Publications

Skog M, Bono P, Lundin M, Lundin J, Louhimo J, Linder N, Petrova TV, Andersson LC, Joensuu H, Alitalo K, Haglund CH. Expression and prognostic value of transcription factor PROX1 in colorectal cancer. Br J Cancer. 2011;105:1346-51.

3.4 The pathobiology of melanoma

1. Molecular characterisation of melanoma progression: the role of BCSC1

Principal Investigator Vincent Piguet

Using state of the art molecular biology techniques the Piguet laboratory has identified a new gene in melanoma, which functions as a tumor suppressor gene: its expression is decreased in human melanoma and melanoma cell lines. When the gene is introduced in melanoma cells, the cells switch from a proliferating to a migratory behavior, which would fit with a role of BCSC in melanoma progression. The characteristics of this gene and its function are further explored in this project.

Understanding the molecular alterations involved in the development and progression of metastatic melanoma is essential for a better diagnosis and targeted therapy In this project we identified BSCS-1 as a novel tumor suppressor in melanoma using a global analysis of alternative splice variants. By using *in silico* analysis of human publicly available microarray data, qRT-PCR and Western blot techniques on human biopsies we could confirm that BCSC-1 expression is decreased in human melanoma and in melanoma cell lines. Moreover, its ectopic expression blocked tumor formation in vivo and melanoma cell proliferation in vitro. We could show that BCSC-1 downregulates MITF at the transcriptional level via its interaction with Sox 10, resulting in a switch of melanoma cells from a proliferative to a migratory phenotype. We thus identified BCSC-1 as a novel regulator of MITF. BCSC-1 could be used as a marker for melanoma progression and prognosis.

Anghel SI, Correa-Rochal R, Budinska E, Boliganl KF, Abraham S, Colombetti S, Fontao L, Mariotti A, Rimoldi D, Ghanem GE, Fisher DE, Lévy F, Delorenzi M, Piguet V. Breast cancer suppressor candidate-1 (BCSC-1) is a melanoma tumor suppressor that down regulates MITF. Pigment Cell Melanoma Res. 2012;25:482-7.

2. New prognostic markers and therapeutic approaches in melanoma

Principal Investigator Ghanem Ghanem

The Ghanem laboratory studies the biology of melanoma, with the intention to identitfy markers which are prognostic (distinguish melanoma with low risk of progression from high risk melanomas) and new therapies for melanoma. A promising new marker is TYRP1, of which the biology is studied in melanoma cell lines. A promising new therapy for melanoma could be Dasatinib. The mechanisms of action of this drug are explored, in order to allow identification of patients which might benefit from Dasatinib treatment.

With regard to the critical problems linked to the management of high risk melanoma patients, we performed a research on 3 axes: (1) the search for new prognosis markers, (2) the evaluation of new target for therapy and (3) the identification of predictive markers for response to targeted drug. First, in order to train classifiers, we used skin and lymph node metastases from melanoma patients to identify candidate prognostic

marker(s) based on DNA microarray analysis and we subsequently validated the prognostic value of the first ranked gene on skin metastases by real-time PCR. We generated a list of 278 probe sets associated with a shorter survival. We used the first ranked gene, tyrosinase-related protein 1 (TYRP1), further measured its expression in the validation population by real-time PCR, and found significantly correlated with DMFS, OS and Breslow thickness. We also found that it was relatively conserved in the course of the disease regardless of the delay to metastasis occurrence. Thus, our data indicate that TYRP1 mRNA expression level, at least in skin metastases, is a prognostic marker for melanoma, particularly useful when prognostic pathology parameters in the primary lesion are lacking. Its conserved expression further supports its use as a target for therapy.

Second, we compared 3 ^{V600E}BRAF-mutated with 3 wild-type (WT) melanoma cell lines addressing ERK phosphorylation, cell proliferation, apoptosis, senescence (β-galactosidase activity), and response to a MEK inhibitor (U0126) in terms of proliferation and senescence. We confirmed that mutated cells exhibited significantly higher levels of ERK1/2 phosphorylation, but, surprisingly, these cells had a 2.5-fold lower proliferation index (day3/day1 ratio). We also found that β -galactosidase activity is higher in mutated cells along with significant increase in cell size (2 fold) supporting that constitutive MAPK hyper-activation induces a senescence-like phenotype. Furthermore, we interfered with the MAPK signaling pathway by long-term exposure of mutated cells to 10^{-6} M MEK inhibitor (U0126) and found that both β -galactosidase activity and cell volume significantly decrease together with a significant increase of the proliferation index. Thus, long-term inhibition of the MAPK may reverse senescence and restore cell growth in mutated cells. These results could bring additional mechanisms of resistance to anti-^{V600E}BRAF therapy.

Finally, we evaluated the effects of dasatinib (BMS-354825, Sprycel) on 21 melanoma cell lines and found that 6 lines were highly sensitive to dasatinib (IC50s < 10^{-9} M), 7 were moderately sensitive (IC50s from 10^{-8} to 10^{-6} M) and 8 were resistant (IC50 > 10^{-5} M). All highly sensitive lines expressed high cKIT, whereas the others had undetectable levels. Importantly, SRC expression was not correlated to cell sensitivity to dasatinib and all highly sensitive lines had no mutation on cKIT, BRAF or NRAS, while 58% of the moderately sensitive and 75% of the resistant cell lines had activating mutations. On the molecular target level, dasatinib dramatically inhibited the phosphorylation of cKIT, SRC, ERK and AKT in sensitive cells, while it had no effect on the phosphorylation of both ERK and AKT in the mutated ones, suggesting a selective effect on proliferation/survival of cells with cKIT expression not harbouring NRAS/BRAF mutation, the latter are likely to render melanoma cells much less dependent on cKIT signalling for their survival. From our data, about 25% of metastatic melanoma patients would highly benefit from dasatinib treatment considering the wide therapeutic window of the drug. Our results bring together three important aspects directly transposable to translational research and may also bring new insights into the biology of melanoma.

Publications

Journe F, Boufker HI, Van Kempen L, Galibert MD, Wiedig M, Salès F, Theunis A, Nonclercq D, Frau A, Laurent G, Awada A, Ghanem G.
TYRP1 mRNA expression in melanoma metastases correlates with clinical outcome.
Br J Cancer. 2011;105:1726-32

Ghanem G, Fabrice J.Tyrosinase related protein 1 (TYRP1/gp75) in human cutaneous melanoma. Mol Oncol. 2011;5:150-5.

Herraiz C, Journé F, Abdel-Malek Z, Ghanem G, Jiménez-Cervantes C, García-Borrón JC. Signaling from the human melanocortin 1 receptor to ERK1 and ERK2 mitogen-activated protein kinases involves transactivation of cKIT.
Mol Endocrinol. 2011 ;25:138-56.

3.5 Immunotherapy of cancer

Immunotherapy of cancer has been an important research focus for several decades and remains to be so. Key questions are: why the immune system responds initially to the presence of abnormal (cancer) cells in the body but fails to eliminate these cells. Conceptually, this might be due to failure of the immune system to recognize the cancer cells as harmful, hence no longer attacking them. Alternatively, this may be due to failure of immune-competent cells to kill the cancer cells. Effective ways to reconstitute and reinforce the immune system in its efforts to eliminate cancer cells would constitute a major breakthrough in cancer research and treatment. Two groups are working in this area, one on melanoma as a model system with emphasis on the role of miRNAs in the regulation of the function of CD8+ T-cells and the other on leukemia, with similar approaches and productive interaction between the groups.

1. **Role of miRNA species in regulating the immune response to melanoma**
   Principal Investigator Pedro Romero

The Romero laboratory studies mechanisms deployed by the immune system to attack cancer cells. The ultimate goal is to develop effective immunotherapies. In this project regulation of the function of a specific set of immune-competent cells (CD8+ T-cells) is examined. It was found that their function is at least in part regulated through micro-RNA, a new species of RNA with important general gene regulatory functions and potentially important as diagnostic tool as well as target for new therapies. The group focuses on melanoma.

We purified CD8+ T-cell subpopulations from healthy human donors and extracted microRNAs. Microarray analysis was performed in collaboration with the group of Ph.Martiat (Inst.Jules Bordet, Brussels) to assess the expression of 365 unique microRNAs in these different subpopulations. Results showed that in all donors, CD8+ T lymphocytes expressed a limited set of microRNAs (less than 100, with 20 being expressed at high levels). Although rather surprising, this low number is comparable with previously published work on B cells and mouse T cells. Among the well expressed microRNAs in the human CD8+ T cell subsets, we found miR-21, miR-142, miR-155 as well as 7 microRNAs of the miR-17-92 cluster. The high representation of this cluster has not been described before, and suggests an important role for these microRNAs in the biology of CD8+ T cells. MicroRNA expression in antigen experienced subsets was then compared to that found in naïve cells, in order to investigate the regulation of expression that may occur during differentiation. Despite inter-donor variability, this analysis showed consistent upregulation of miR-21, miR-146a and miR-155 in antigen-experienced cells, with a clear trend towards higher

expression in the most differentiated subsets. By contrast, the 17-92 cluster was downregulated in antigen experienced cells, while a preferential downregulation of the miR181 cluster was observed in the EM28+ 'central memory like' subset. Interestingly, a similar trend could be observed in MelanA specific CD8 T cell clones derived from melanoma patients, with EM 28+ clones expressing lower levels of miR181a than EM28- ones.
Similar experiments were carried out in parallel in mouse lymphocytes, using the LCMV infection model as a source of in vivo activated effector cells. The results obtained in human cells could be recapitulated in this model, indicating a conserved mechanism likely to have a physiological relevance for the function of differentiated lymphocytes.
Thus, we could show that in vivo differentiation of CD8+ T lymphocytes is associated with specific modulation of the microRNA expression pattern in both mouse and human.

Publications

Baitsch L, Baumgaertner P, Devêvre E, Raghav SK, Legat A, Barba L, Wieckowski S, Bouzourene H, Deplancke B, Romero P, Rufer N, Speiser DE. Exhaustion of tumor-specific $CD8^+$ T cells in metastases from melanoma patients.J Clin Invest. 2011 1;121:2350-60

Sierro SR, Donda A, Perret R, Guillaume P, Yagita H, Levy F, Romero P. Combination of lentivector immunization and low-dose chemotherapy or PD-1/PD-L1 blocking primes self-reactive T cells and induces anti-tumor immunity. Eur J Immunol. 2011;41:2217-28

Salaun B, Yamamoto T, Badran B, Tsunetsugu-Yokota Y, Roux A, Baitsch L, Rouas R, Fayyad-Kazan H, Baumgaertner P, Devevre E, Ramesh A, Braun M, Speiser D, Autran B, Martiat P, Appay V, Romero P. Differentiation associated regulation of microRNA expression in vivo in human CD8+ T cell subsets. J Transl Med. 2011;9:44.

2. The role of the immune response in leukemia development

Principal Investigator Philippe Martiat

Like the Romero laboratory, the Martiat laboratory studies mechanisms deployed by the immune system to attack cancer cells. The high incidence of relapse in human cancers demonstrates the failure of the immune system to control cancer cells naturally. Fundamental investigations in the last decades have clearly established the concept that crosstalk between the immune system and tumor cells is important in cancer patient outcome. Tumors develop many ways to escape immune surveillance and favor their own growth. Even when a potent immune response is demonstrated ex vivo in laboratory, tumors induce regulatory, suppressive and inhibitory mechanisms to protect themselves from this immune response in patients. The interplay between the tumor and her immune microenvironment has been recently defined as a key element in the goal to achieve a definitive cure in cancer patients. The primary objective of our project is to understand in details the mechanisms responsible for the lack of effective anti-tumor immune response in leukemia.

Our approach is to characterize the functionality of the immune system of leukemic patients in order to define reliable, relevant and cost effective immune signatures. These immune profiles will help us to determine firstly which group of leukemic patient could benefit from immunotherapeutic approaches to eradicate leukemic cells and secondly to follow the patient treatment response and risk of relapse.

Our group focuses on the influence of tumor environment on cancer cells, using acute human leukemia (AL) and the immune environment as a model. We are working at two levels: the first is the study of the function of regulatory T cells (Tregs) in leukemic patients peripheral blood. Since the tools -molecular mechanisms controlling the regulatory function- were not available, we had first to characterize these mechanisms in the various Treg types in healthy persons, before starting the comparison with patients. We have now started this last step, and have collected samples from patients and tested some that revealed differences with healthy individuals' Tregs. However, this last work is very preliminary and need more patients to ascertain our results. The second level of investigation consists of characterizing the whole T cell compartment (using transcriptomic methods) by selecting bone marrow and PB CD3+ lymphocytes at diagnosis and in remission after chemotherapy. The questions are different and more global than the part dedicated to the Tregs. They could be summarized as follows: How do T cells infiltrating the bone marrow and the blood of the leukemic patients compared to normal volunteers? Were there differences, particularly in B ALL that could be related to the different outcome in children (1 – 10 years old) and adults, whose outcome is different? Is the profile of circulating T cells similar to bone marrow T cells? What happens in AML, are there different sub-population patterns, which could ultimately be related to leukemia free survival?

In order to explore the potential implication of microRNAs in CD8+ T cell differentiation in humans, microRNA expression profiles were analysed using microarrays and quantitative PCR in several human CD8+ T cell subsets defining the major steps of the T cell differentiation pathway.We found expression of a limited set of microRNAs, including the miR-17~92 cluster. Moreover, we revealed the existence of differentiation-associated regulation of specific microRNAs. When compared to

naive cells, miR-21 and miR-155 were indeed found upregulated upon differentiation to effector cells, while expression of the miR-17~92 cluster tended to concomitantly decrease.

Regulatory T cells (Tregs) are characterized by a high expression of IL-2 receptor α chain (CD25) and of forkhead box P3 (FOXP3), the latter being essential for their development and function. Another major player in the regulatory function is the cytotoxic T-lymphocyte associated molecule-4 (CTLA-4) that inhibits cytotoxic responses. However, the regulation of CTLA-4 expression remains less well explored. We therefore studied the microRNA signature of circulating CD4(+) Tregs isolated from adult healthy donors and identified a signature composed of 15 differentially expressed microRNAs. Among those, miR-24, miR-145, and miR-210 were down-regulated in Tregs compared with controls and were found to have potential target sites in the 3'-UTR of FOXP3 and CTLA-4; miR-24 and miR-210 negatively regulated FOXP3 expression by directly binding to their two target sites in its 3'-UTR. On the other hand, miR-95, which is highly expressed in adult peripheral blood Tregs, positively regulated FOXP3 expression via an indirect mechanism yet to be identified. Finally, we showed that miR-145 negatively regulated CTLA-4 expression in human CD4(+) adult peripheral blood Tregs by binding to its target site in CTLA-4 transcript 3'-UTR. To our knowledge, this is the first identification of a human adult peripheral blood CD4(+) Treg microRNA signature. Moreover, unveiling one mechanism regulating CTLA-4 expression is novel and may lead to a better understanding of the regulation of this crucial gene.

Publications

Fayyad-Kazan H, Rouas R, Fayyad-Kazan M, Badran R, El Zein N, Lewalle P, Najar M, Hamade E, Jebbawi F, Merimi M, Romero P, Burny A, Badran B, Martiat P. MicroRNA profile of circulating CD4-positive regulatory T cells in human adults and impact of differentially expressed microRNAs on expression of two genes essential to their function.J Biol Chem. 2012;287:9910-22.

Salaun B, Yamamoto T, Badran B, Tsunetsugu-Yokota Y, Roux A, Baitsch L, Rouas R, Fayyad-Kazan H, Baumgaertner P, Devevre E, Ramesh A, Braun M, Speiser D, Autran B, Martiat P, Appay V, Romero P. Differentiation associated regulation of microRNA expression in vivo in human CD8+ T cell subsets.
J Transl Med. 2011 20;9:44.

4. Outlook

The way the MEDIC foundation supported consortium 'Tumor-host interaction' continues to evolve confirms that high quality research can be supported in an approach that is not competitive in the sense of the usual research grant providing institutions (National Research Foundation, Swiss Cancer League). A high standard continues to be reached through auto-evaluation, internal review within the consortium and external peer review of new applications. The research program continues to support the development of new interactions and new research directions that the individual groups alone would not have made so easily are entertained, as the new requests for 2012 submitted in 2011 will show. External peer review of the consortium constitutes a significant effort but remains an essential step towards a scientifically valid modus operandi. The independent external Scientific Advisory Board has been created (prof. F.Lejeune, prof.G.Christofori, prof. H.Moch, prof. M.Mareel), which has evaluated the overall performance of the groups, in participating (in part) in the annual research meeting and evaluating the annual reports submitted by the groups, and of the consortium as a whole. The board members have functioned as reviewers and as jury in the MEDIC prize applications. The trustees have confirmed their satisfaction with the choices made and the structures developed and have confirmed their intention to continue to support the consortium to the extent of the possible at the present level.
The Foundation does not seek a high profile but more explicit visibility of MEDIC through its research support would be desirable. An important element is here the obligation of investigators supported by MEDIC to specifically mention MEDIC support in their publications. In addition a website is under development (has effectively gone live in nov. 2012 www.fondation-MEDIC.ch), allowing MEDIC member groups to remain informed as to the activities of the consortium. More importantly, the site will increase visibility of the Foundation and allow Foundation Trustee members to follow more closely the research activities deployed. The 'MEDIC prize' for a particularly promising young clinician scientist, which was awarded for the first time in 2010, has been awarded in 2011 to dr. Anita Wolfer from Lausanne. A call for applications for the 2012 prize has gone out and several high quality applications have been received.

Fred T Bosman
Lausanne
November 2012