FONDATION
MEDIC

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

Annual Report 2008

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1. Introduction

The consortium, created in 2006 around the project groups funded by grants from the MEDIC Foundation, has continued to flourish. In terms of administrative functioning the change in approach – only peer reviewed grants and no longer "structural" institutional funding – was completed and presently all subsidies are based upon a peer reviewed grant. Annual scientific and financial reports are received (a condition for continued funding). The consortium members 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 programme of the 2008 meeting is presented in table 1.

Table 1: Scientific programme MEDIC day 2008

V.Piguet	Gene expression profiling of pigmented skin lesions and primary melanoma
A.Mariotti	Study of the role of lactadherin in melanoma progression
G.Ghanem/ F.Journe	New treatments, new markers in melanoma
C.Ruegg	Unraveling heterotopic interactions in the tumor micro-environment
GC.Alghisi	Bone marrow and peripheral blood cells in human cancer: use for diagnostic, prognostic and therapeutic purposes
I.Stamenkovic	Tumor-host interactions in cancer progression and metastasis
M.Delorenzi	In silico modeling of tumor stroma
C.Sotiriou	Integrating tumor microenviroment, micrometastasis and the host properties in the study of breast cancer progression.
T.Petrova	Analysis of PROX1 role in colon and small cell lung cancers
P.Martiat	Leukemia-host interactions: interplay between leukemic cells, marrow immune and mesenchymal stem cells
P.Romero	Role of microRNA's in CD8 T-cell function

Intensive 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. Several new groups have been incorporated in the consortium over 2008 and restructuring of long standing research projects, focusing more on possible synergies between groups, has been accomplished.

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

PI	Project title		Budget 2009
C.Ruegg	Unraveling heterotypic interactions in the tumor micro-environment	CHF	311'440.-
A.Mariotti	Study of the role of lactadherin in melanoma progression	CHF	153'095.-
D.Picard	Mechanisms and functions of unusual estrogenic signaling by the host and the environment in breast cancer	CHF	173'720.-
M.Delorenzi	Tumor expression profiling In silico modeling of tumor stroma	CHF	120'240.-
V.Piguet	Molecular pathways in melanoma progression	CHF	
GC. Alghisi	Study of bone marrow-derived peripheral blood cells in human cancer progression: evaluation of their potential use for prognostic, diagnostic and therapeutic means.	CHF	103'000.-
T.Petrova	Analysis of PROX1 role in colon and small cell lung cancers	CHF	168'000.-
I.Stamenkovic	Tumor-host interactions in cancer progression and metastasis	CHF	83.000.-
P.Romero	Role of microRNAs in CD8 T cell function	CHF	112’012.-
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 interactions	€	226'864.-

It is relevant here to note that the total volume of MEDIC supported research conducted in Lausanne has grown and presently 8 groups profit from MEDIC support. 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 projects groups. Geneva participates with 2 groups.

3. Scientific reports

Signatures predictive for response to chemotherapy in breast cancer (R. Iggo; M. Delorenzi)

In 2008, the project focused on the biological interpretation of the signature which we previously found associated with response to chemotherapy. We had analyzed gene expression profiles from 102 pre neo-adjuvant treated breast cancer biopsies with known pathological complete response (PCR) status and found that high expression of a "stroma" metagene was associated with resistance to the FEC chemotherapy regimen in the subset of ER negative tumors. Histologically, there were striking differences between tumors in the amount of reactive stroma, and this was strongly associated to the expression of the stromal metagene.

To confirm that the genes in the stromal metagene are expressed by stromal cells in the tumor compartment, we analyzed public data generated by microdissection of breast tumors (GSE5847). To determine whether a gene was expressed preferentially by epithelial or stromal cells, we calculated an epithelial to stromal ratio for each gene. The stromal metagene showed a low epithelial – stromal ratio, consistent with the constituent genes being expressed primarily in the stroma.

To explore the biology underlying the stromal metagene, we compared it to several potentially relevant gene lists notably in the Wnt signaling pathway and in EMT. Gene Set Enrichment Analysis supports a potential role for both processes in reactive stroma. We conclude that reactive stroma is intrinsic to tumors that are resistant to FEC, and this may arise from activation of TGFb or Wnt signals. A paper has been published in Nature Medicine.

Publications

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Integrating tumor microenvironment, micrometastasis and host properties in the study of breast cancer progression
(C. Sotiriou)

We were able to isolate tumor-associated CD10+ cells as well as CD10+ samples from several tumor and normal breast tissues. Genome-wide gene expression analysis of these cells confirmed earlier findings of several changes in the gene expression patterns between tumor-associated CD10+ cells and their normal counterparts. From this analysis a CD10-stromal signature was developed and its prognostic performance was further investigated on publicly available microarray breast cancer datasets. These genes are involved in matrix remodeling, such as MMP13, MMP11, ADAM12, and, surprisingly, genes related to "osteoblast differentiation", such as periostin. From this comparison, a CD10+ stromal signature was developed and its association with the current molecular classification and clinical outcome was assessed.

Hierarchical cluster analysis of the tumor-associated CD10+ cells partitioned these cells into clusters according to the molecular subtypes of the corresponding tumors from which they derived. This suggests that the expression pattern of stromal cells may differ according to the molecular subtypes of breast cancer. We hypothesize that cross-talk of tumor epithelial-stromal cells and/or their molecular alterations ((epi-)genetics) may be involved in the development of the breast cancer molecular subtypes.

The prognostic value of the CD10+-stromal signature was studied by retrospectively analyzing available microarray data generated from whole tumors of more than 2000 patients. Interestingly, an "activated" stromal signature was associated with poor clinical outcome in the HER2+ subpopulation only. These findings suggest that a stromal signal can be detected in expression data generated from whole tumors and that a stromal signature could provide more information than other prognostic signatures.

We recently performed a comprehensive meta-analysis of gene expression signatures integrating both clinico-pathological and gene expression data and focusing on the main molecular subtypes. We developed gene expression modules related to several key biological processes in breast cancer such as tumor invasion, immune response, angiogenesis, apopotosis, proliferation, ER and HER2 signaling, and then analyzed these modules together with clinical variables and several prognostic signatures on publicly available microarray datasets (>2100 patients). Interestingly, and similar to our CD10+ signature, our in silico-developed tumor invasion module was highly prognostic in the HER2+ subgroup only. Although this tumor invasion module and the CD10+ stromal signature were developed using a completely different approach, they were highly correlated.

Since our CD10+ stromal signature included genes involved in osteoblast differentiation such as periostin, we investigated the expression of this protein in several primary tumors. Interestingly, we observed that some tumors showed high levels of this protein.

We then investigated the expression of alkaline phosphatase, an enzyme produced by osteoblasts that has a role in the mineralization of bon,e in primary breast cancer tissue samples. Some cases with high expression levels of alkaline phosphatase were found. Consequently, the CD10+ fraction may encompass more cell types than initially thought, including mesenchymal stem cells (MSC). We suggest a strong role for MSC in breast cancer progression.

Given these intriguing preliminary results and considering the potentially crucial role of MSC in breast cancer progression, we aimed to identify cell surface markers that would allow us to discriminate MSC from the other CD10+ cells. FACS analysis in cultured myoepithelial, fibroblast and MSC cells identified CD105 as a potential candidate MSC marker. In particular, FACS analyses of normal and tumor CD10+ stroma cells revealed the presence of CD105+ cells only in the tumor CD10+ component.

Publications

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Mechanisms and functions of unusual estrogenic signaling by the host and the environment in breast cancer
(D. Picard)

The project has three research lines:

1. Estrogen signaling through the membrane receptor GPR30
The membrane-bound estrogen receptor GPR30 mediates the stimulation of proliferation by estrogen of several cell lines representing different types of carcinomas independently of the presence of estrogen receptor α (ERα) or estrogen receptor β (ERβ). Our most recent results contribute to understanding its pharmacology, regulation, and biological function.

- To facilitate the pharmacological and structure-function analysis of GPR30, we have begun to reconstitute this signaling pathway in the budding yeast.
- We found that GPR30 expression is induced by EGF (Albanito et al., 2008), which suggests that estrogenic signaling through GP30 may be embedded in a network of positive and negative feedback control circuitries.
- We have discovered that GPR30 signaling induces connective tissue growth factor (CTGF), which then stimulates the proliferation and migration of ER-negative (or most likely ER-positive) breast cancer cells (Pandey et al., 2009). Since GPR30 signaling can also be elicited by the antiestrogen tamoxifen these findngs suggest that tamoxifen might be deleterious in COR30 positive breast tumors.

2. Mechanism and consequences of activation of ERα by cAMP signaling
For many years we have been studying how ERα is activated by other signaling pathways, notably growth factors and factors that lead to elevated intracellular cAMP.
We found that cAMP stimulates the phosphorylation of the ERα coregulator CARM1 allowing it to bind directly to ERα in the absence of estrogen. Binding is necessary but not sufficient, suggesting that there might be additional factors. By comparing wild-type and tamoxifen-resistant MCF7 breast cancer cells, we found that CARM1 is constitutively phosphorylated and binds ERα in tamoxifen-resistant cells. This argues that this type of signaling crosstalk may contribute to the tamoxifen resistance of certain breast cancers. Furthermore, we found that different ERα activators elicit vastly different genomic responses in breast cancer cells, and thus presumably physiological effects (Dudek and Picard, 2008).

3. A microRNA inhibits estrogen signaling
ERα signaling being critical for a number of physiological and pathological processes, it is obvious that ERα levels must be tightly controlled. We therefore performed a comprehensive and systematic assessment of all microRNAs that might regulate Erα expression by targeting the 3'UTR of its mRNA. We found that miR-22 represses Erα expression. As a consequence, miR22 overexpression diminishes Erα-mediated proliferation of MCF7 breast cancer cells (Pandey and Picard, 2009).

Publications

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Pandey DP, Lappano R, Albanito L, Madeo A, Maggiolini M, Picard D. Estrogenic GPR30 signalling induces proliferation and migration of breast cancer cells through CTGF. EMBO J. 2009;28:523-32.

Lactadherin in melanoma progression
(A. Mariotti)

We have performed experiments to characterize the function of lactadherin in melanoma cells. We obtained the following results.

1. Expression of this protein is heterogeneous between tumors and not correlated to the stage of tumor progression. This is in line with previous data of lactadherin expression in melanoma cell lines. We assume that the protein is differentially secreted, probably as a result of the cells' ability to translocate it to membrane rafts. Immunohistochemistry on tissue microarrays showed that lactadherin is present in a subset of tumors, some of which are strongly and homogeneously positive throughout the whole samples, while others express the protein only in some areas. We will further analyze lactadherin expression in biopsies of nevi, and of primary and metastatic melanomas from the same patients. This will indicate if lactadherin expression is increased in benign naevocellular lesions, and if it is regulated during melanoma progression.

2. We have overexpressed lactadherin in the RFP cell line SBC12, which increased tumorigenicity after injection in nude mice. Overexpression of lactadherin in another RGP cell line, WM35, resulted in tumors with unchanged kinetics relative to non-lactadherin expressing cells. However, WM35 secrete lactadherin constitutively which might obscure an effect of lactadherin overexpression in terms of growth advantage. Similar experiments on non-lactadherin expressing tumorcells are ongoing. We have generated melanoma cells with decreased expression of lactadherin through shRNA. Cells will be injected subcutaneously in nude mice and their ability to form tumors will be evaluated.
   In summary, lactadherin is expressed in some melanomas; overexpression of lactadherin in cultured cells promotes tumorigenesis depending on the cell line.
3. We are presently studying the mechanisms involved. We have started to examine the role of lactadherin in breast carcinomas. We found that lactadherin expression is strongly associated with the aggressive basal-like breast carcinomas. Knockdown of lactadherin expression in MDA-MB23 cells that have basal-like characteristics through shRNA showed that decreased lactadherin expression reduces cell growth in mice mammary fat pads. Studies of lactadherin expression in biopsies of basal-like breast carcinomas in comparison with biopsies of estrogen receptor positive and of triple negative, non-basal-like tumors are ongoing.

Publications

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Role of a novel tumor suppressor identified by DATAS in melanoma progression (V. Piguet)

Using DATAS (Differential Analysis of Transcripts with Alternative Splicing), we identified a total of 217 sequences that are differentially expressed in metastatic melanoma and benign nevus. Out of several candidates that we screened this year we identified a potential novel tumor suppressor gene (TS1) implicated in metastatic melanoma.

RNA expression analysis by quantitative PCR demonstrates that TS1 is down regulated in all patients with stage IV disease in comparison with the expression observed in benign nevus. Ectopic expression of this gene in melanoma cell lines using a lentivector decreases markedly the proliferation of these cells. In vivo experiments are ongoing and show that B16 melanoma cells transduced with TS1 induce significantly less metastasis than control cells. Furthermore, our results demonstrate that this gene appears to block the proliferation of melanoma cells in the G2/M phase of the cell cycle. Current experiments aim to further understand the function of this gene in melanoma progression. We will test in the near future the capacity of the gene to control tumor invasion versus proliferation.

Molecular pathways of melanoma progression (G. Ghanem)

The project has focused on three topics.

1. Gene expression profiling towards defining prognostic signatures in melanoma

   By microarray analysis (Affymetrix technology) we found significant differences between primary tumors and lymph node metastases, suggesting that there is no major influence of the organ microenvironment on the gene expression profiles of tumor cells.
   We developed a "Breslow signature" (50 up and 50 downregulated genes, 66 known genes). The median score of high Breslow tumors (>3 mm) was significantly different from low Breslow (< 3mm) tumors indicating that the signature discriminates between these 2 groups. The signature correlates with distant metastasis-free survival (DMFS) of primary tumors but not in the LN metastasis group.
   Two genes in the signature are associated with pigmentation: tyrosinase-related protein 1 (TYRP1, 57.8x) which codes for one of the main melanogenesis enzymes, and oculocutaneous albinism II (OCA2, 8.6 x) which codes for a tyrosine transporter (tyrosine being the precursor of melanins). Interestingly, TYRP1 tended to correlate with the DMFS in the SK group and then appears as a strong element of the "Breslow signature". Moreover, TYRP1 was significantly higher (Mann Whitney, p=0.022) in SK subpopulation with a shorter DMFS (<12 months) than in SK subgroup with a longer DMFS (>12 months).

2. BRAF mutation and oxidative stress in melanoma tumor progression

   Our preliminary results revealed that 1) the proliferation index is lower in mutated than in ^{WT}BRAF cells, 2) MTBRAF cells express higher levels of P-ERK and DUSP6 than ^{WT}BRAF cells, suggesting that the activation of the MAP kinase pathway could be better controlled by phosphatases in this case, and 3) DIGE analysis revealed protein levels that could be the consequence of the BRAF mutation (change in oxidative stress, increase of apoptosis).

3. Specific drug delivery using melanoma associated proteases

   Extensive in vitro and in vivo experimental studies strongly suggest that not only melanoma tumor cells and tumor sites but other types of tumors as well may be targets for the toxic activity of prolyl-m-sarcolysyl-p-fluorphenylalanine (PSF) owing to their much higher load in proteolytic enzymes that are closely related to their invasive potential. The transport of PSF by the blood cells and the release of its metabolites at the tumor site result in a low amount of drug in its free soluble form within the blood and this may explain the relatively lower side-effects observed. PSF is thus expected to have a much better therapeutic index than conventional alkylating agents. This original mechanism of drug delivery may well be extended to other cancer and non-cancer drugs than alkylating agents.

Publications

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Unraveling heterotypic interaction in the tumor microenvironment
(C. Ruegg)

The project has three main aims:

1. Role of PKB and COX-2/Celecoxib-modulated genes in endothelial and cancer cell autonomous and paracrine communication

   Role of PKB-modulated genes: We have tested the effect of PKB target genes in modulating the behavior of neighboring cancer cells. To this purpose we have generated endothelial cells (HUVEC) expressing wt-PKB, active PKB and dominant negative PKB through lentiviral vector transduction. Tumor cells were transduced with GFP-expressing lentivector to generate "green" cell lines. We observed that HUVEC expressing activated Akt (myrAkt) consistently promote the invasion of tumor cell spheroids into the surrounding gel compared to HUVEC expressing wt Akt.
   We also observed that endothelial cell cultures on Matrigel form tube-like networks and that tumor cells rapidly (within one day) associate with them. In co-cultures with activated endothelial Akt, the tube-like structure had a different, less differentiated morphology, and tumor cells dissociated from endothelial cells to invade the surrounding matrix.
   We concluded that the Akt status in endothelial cells modifies the behavior of juxtaposed tumor cells favoring their invasion into the surrounding matrix; non activated endothelial cells might retain tumor cells in a non invasive state.

   Role of Cox-2-modulated genes: Gene expression profiling of HUVEC cells after celebrex treatment identified several interesting candidate of which the COX-2 induced regulation was further analyzed and validated in cancer cell lines by RT-PCR or Western blotting. Three proteins were retained for further analysis: MAGI1, KLFY AND SPARC.
   MAGI1, a scaffolding membrane protein that binds to β-catenin, stabilizes adherens junctions and recruits PTEN to cell-cell contacts. Modulation of MAGI1 protein levels, induced changes in cell morphology and completely inhibited cell migration and invasion in the colon carcinoma cell lines overexpressing MAGI1 (HCT116 and SW480). We are now analyzing Wnt transcriptional activity and beta catenin localization in cell lines with altered MAGI1 expression and the role of MAGI1 in vivo.
   KLF4, a zinc finger transcription factor whose expression is reduced in many tumors
   SPARC, a matricellular protein that modulates growth factor activity, MMP expression, cell adhesion and migration.

2. Identification of PKB/Akt-induced gene expression programs in melanocytes, epithelial, stromal and inflammatory cells
   This aim was not initiated yet..

4. The role of CYR61 in multistep tumor progression
   To address this question we have generated transgenic mice expressing wtCYR61 or CYR61 fused with RFP protein in the beta cells of the pancreas (Rip1::CYR61). We have obtained several founders that were normal, fertile and able to pass the transgene to a second generation of mice. Expression of the transgene in the pancreas was confirmed by RT-PCR. We are expanding the colonies for analysis of possible local effects in the pancreas (cell growth, angiogenesis, invasion) and also crossing them with Rip1Tag2 mice to generate mice developing beta cell tumors concomitantly expressing CYR61.

These mice will be monitored for metastasis formation, a rare event in regular Rip1Tag2 mice and obtained founders. These mice will be analyzed for survival, local tumor progression (growth, angiogenesis, lymphangiogenesis, invasion) and in particular for metastasis formation (LN, liver, lung).
In a second model, we have tracked metastasis derived from murine 4T1 breast cancer cell-derived tumors implanted orthotopically in the mammary fat pad of immunocompetent or immunosuppressed mice. Tumor cells were tagged with Luciferase, to allow monitoring local growth and metastatic dissemination. Strikingly we observed a mouse strain dependent metastatic capacity and the development of a brain metastatic phenotype by repeated injection of cells derived from brain metastases. We analyzed CYR61 expression and observed that brain metastasis prone cells expressed 7-10 time higher levels of CYR61 compared to the parental line. This is the first described model of orthotopic breast cancer metastasizing spontaneously to the brain.

Publications

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Leukemia-host interactions: interplay between leukemic cells, marrow immune and mesenchymal stem cells (P.Martiat)

a. Immunomodulatory effects of mesenchymal stem cells

Mesenchymal stromal cells (MSC) possess immunomodulatory properties and are successfully used in vivo for controlling graft-versus-host disease (GVHD). Different immune cells are targeted by MSC involving cell contact-dependent or independent mechanisms. However, these effects, especially on T-cells, are not fully understood yet. We investigated this on purified T-cells from adult peripheral and cord blood and the impact of cell to cell ratio in determining MSC activities, using T-cell proliferation in response to different stimuli. We found that MSC induced a dose- and contact-dependent inhibition of T-cell proliferation. Naive (cord blood) T-cells were less sensitive to MSC inhibition than peripheral blood cells. At low concentration, MSC stimulated T-cell proliferation rather than inhibiting it. The stimulation of T-cell proliferation was contact independent. MSC-derived IL-6 was the major cytokine responsible for this effect. These results demonstrate the crucial importance of MSC/T-cell ratio to either support or inhibit T-cell proliferation, and the critical role of IL-6. We then evaluated the inhibitory activity of MSC on purified T-cell proliferation at various MSC/T-cell ratios, concentrating on the requirement for direct contact, the impact of paracrine mediators and MSC conditioned media (CM), recombinant IL10 and anti-IL10 neutralizing antibodies. We found that a cross-talk between MSC and T-cells is crucial for activating MSC immunosuppressive functions and the release of inhibitory factors. We were able to show that IL-10 can act as an activator of the MSC immunosuppressive function.

b. Regulation of Foxp3 and human regulatory T-cells.

How regulatory T cells mediate dominant tolerance is a subject of considerable debate at the moment. We investigated the micro-RNA (miR) signature of human Tregs, using CD4-positive, CD25-positive non-activated T-cells originating from cord blood of uninfected newborns. A signature composed of five miRs (21, 31, 125a, 181c and 374) was identified, of which two were considerably under-expressed (miR31 and miR125a). We identified a functional binding site for miR31 in the 3' UTR of the Foxp3 mRNA. We performed co-transfection experiments in Hela and 293T cells, and could demonstrate a direct regulatory effect of miR31, mediated via this site. Further experiments await the development of lentiviral vectors, which is currently in progress. MiRNA31 was found to be involved in the regulation of Foxp3 gene expression but other mechanisms must contribute to the level of expression. Studying the potential involvement of the Ets family of transcription factors we found that Ets1 and Ets2 play a positive role in the regulation of Foxp3 expression.

c. Pre-clinical studies to optimize the generation of fully functional APCs

We have previously investigated the role of different maturating agents on functional aspects of mature dendritic cells (DC) by comparing different maturation stimuli for their ability to reproducibly generate stable mature DC secreting high amounts of bioactive IL-12. We could confirm that DC, having already produced high amounts of IL-12p70 during the maturation step, are still capable of secreting IL-12p70 after in vivo administration at the time of interaction with the targeted T cell. but only when poly (I:C) is used as the maturating agent.

A finding with important practical implications is the fact that DC generated in bags and then elutriated secreted much less bioactive IL-12 than DC's generated in plates. We found the activation status of Erk to be markedly decreased in DCs generated in plates, with is consistent with an increase in IL-12 secretion. Preliminary results of the micro-array analysis give a hint that plates favor a pathway leading to activation of TH1 T-cells.

d. Effects of global Tregs removal on in vitro generation of anti-WT1 responses
Experiments using WT1 protein loaded APCs and T-cells from a small number of WT1 positive-patients, with or without aspecific depletion of T-Regs, strongly suggest that specific responses are drastically amplified after Tregs depletion. This finding justifies our to focus on the molecular and cellular study of Tregs, in the context of the global topic "Host tumor interactions".

Publications

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4. Financial status

Table 3 presents the balance of the MEDIC account as kept by the Lausanne Cancer Center over 2006-2009.

Table 3 status of the MEDIC accounts

	31.07.2009 CHF	31.12.2008 CHF	31.12.2007 CHF	31.12.2006 CHF
Fonds Cancer du sein Fds Médic				
Solde au 01.01.	1'134'958.46	95'314.62	1'826'775.33	1'271'523.68
Versement de la Fondation Médic	869'360.00	2'740'221.00	20'000.00	1'200'000.00
Versement ISREC	-	7'060.30		
Revenue des intérêts sur cc	1'403.11	16'106.04	10'712.93	6'323.66
Frais divers	-9.87	-11'714.12	-7'747.22	-12'369.45
Versement pour fonds de recherche	-1'929'774.88	-1'599'078.13	-755'295.24	-104'903.46
Charges salariales	-	-31'951.25	-699'131.18	-533'799.10
Transfert de Fonds	-	-81'000.00	-300'000.00	0.00
Solde au 31.12.	**75'936.82**	**1'134'958.46**	**95'314.62**	**1'826'775.33**
Versement engagement pris 2008		-617'697.88		
		517'260.58		
Fonds Cancer du sein Fds Médic EURO				
Solde au 01.01.	68'951.32	-	0.00	0.00
Versement de la Fondation Médic Euros	742'864.00	558'086.00	0.00	0.00
Revenue des intérêts sur cc	180.11	750.05		
26421 Fds Compensations EURO/CHF	-4'512.46	22'360.84	0.00	0.00
Frais divers	-508.39	-6'144.37	0.00	0.00
Versement pour fonds de recherche	-739'880.22	-506'101.20	0.00	0.00
Solde au 31.12.	**67'094.36**	**68'951.32**	**0.00**	**0.00**

The data indicates that the financial buffer, that was accumulated up to 2008, allowed reduction of the MEDIC support over 2009. This has brought the accounts back to financial equilibrium. For the consortium to operate comfortably, some reserves are necessary. But these will not exceed 5-10% of the annual budget.

5. Outloook

It is clear that the resources the MEDIC foundation can make available depend on the revenue generated from the capital of the foundation and that with the difficult economical situation there is no guarantee that the present level of support can be maintained. Nonetheless, the trustees have confirmed their intention to continue to support the consortium to the extent of the possible at the present level. The trustees are satisfied with the present structure: financing of research project that are peer reviewed rather than ad hoc financial support without a tangible project. The funds available will allow some latitude in supporting ad hoc activities. The presently followed procedures for peer review and evaluation of the projects are relatively light, in response to the wishes expressed by the trustees. Nonetheless, strict quality control of the conducted research is essential in order to maintain an internationally competitive level. Therefore, the creation of an international advisory board needs to be considered. This is an important issue, as the structure chosen is that of a self controlling consortium, whereas the generally accepted approach towards maintaining a competitive level is open competition. The trustees have, however, explicitly indicated that open competition, that would need a costly administrative infrastructure, is not what the foundation had in mind. Strict self-control is therfore necessary.
The Foundation does not seek high visibility but more explicit visibility of MEDIC through its reasearch support would be desirable. An important element is here the obligation of investigators supported by MEDIC to specifically mention MEDIC support in their publications. Another approach would be the creation of a 'MEDIC fellowship', salary support and a small running budget for a particularly promising young scientist. This programme will be implemented in 2009.

Fred T Bosman
Lausanne
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