SWISS BRIDGE

INVEST IN CANCER RESEARCH WORLDWIDE

12th SWISS BRIDGE AWARD: 500,000 francs for outstanding cancer research

Summaries of the three supported research projects

Professor Jürg Schwaller, MD, Department of Biomedicine, University Hospital Basel, receives 175,000 Swiss francs for the project entitled:

Modeling for targeting of mixed-lineage acute leukemia
Infant acute leukemia is a rare but severe disease that affects about 5 of 100,000 newborns per year. In almost 80 % of the cases, the leukemic cells harbor chromosomal translocations affecting the mixed lineage leukemia (MLL) gene. Such alterations are also found in pediatric and adult acute leukemia and are often associated with a poor prognosis. These chromosomal translocations lead to the expression of chimeric proteins fusing the amino-terminal portion of MLL to the carboxy-terminus of the partner. Two third of the cases are covered by translocations t(9;11), t(11;19) or t(4;11) leading to MLL-AF9, MLL-ENL and MLL-AF4. Experimental studies have shown that MLL fusions act as potent oncogenes. Gene expression profiling revealed deregulation of closely overlapping downstream targets in human and murine MLL leukemia defining the mouse as an ideal model to study the biology of the disease and to search for novel therapeutic strategies.

Professor Shai Izraeli, MD, Department of Pediatric Hemato-Oncology and Cancer Research Center, Sheba Medical Center, Ramat Gan, Israel, receives 150,000 Swiss francs for the project entitled:

From inflammation and allergy to high risk childhood leukemia – The TSLP-JAK-STAT leukemogenic pathway
Acute lymphpblastic leukemia (ALL) is the most common cancer in children. The major challenge in management of childhood acute ALL is to increase cure rate with lesser toxicity through the identification of biomarkers amenable to targeted therapies. This proposal is based on our discovery of the aberrant expression of the receptor to thymic stromal lymphopoietin (TSLP) in childhood ALL with particularly poor prognosis. Importantly this abnormality is amenable to targeted therapy with JAK and mTOR inhibitors and clinical trials have already started, barely three years from our first report. We further discovered that the aberrant activation of this receptor is caused by a complex array of cooperating mutational events including genomic translocations, unique activating mutations in its key component CRLF2 and IL7 receptor (IL7R) and mutations in downstream enzymes (JAK1 and JAK2). Yet it is presently unclear how these successive mutations affect the initiation and progression to leukemia, what is their relative importance for leukemia evolution and what are their specific oncogenic roles, separately from the effects of other leukemia oncogenes.

To elucidate these questions we will create a model of gradual transformation of human cord blood hematopoietic progenitors by expressing one or more of the mutated proteins. Utilizing B cell cultures we will examine B cell differentiation, proliferation, survival and self renewal as well as downstream targets *in vitro* and generation of pre-leukemia and leukemia *in vivo* by transplantation of transduced CB progenitors into NOD/LtSz-scid IL2Rγnull (NSG) mice. We will also unfold the potential differential activity of “lymphoid” vs “myeloid” JAK2 mutations. Utilizing a primary human model system we hope to answer two key questions in leukemia

research: (a) What is the role of an aberrant activation of inflammatory TSLP pathway in evolution of ALL? This may be particularly important to the general theme of environment and health as childhood ALL has been proposed to evolve by an abnormal immune response to early childhood pathogens. TSLP may be the “missing link”; and (b) what are the downstream components of the TSLP pathway in leukemia that may be receptive to targeted therapy.

Professor Monika Hegi, PhD, Laboratory of Tumor Biology and Genetics, Department of Neurosurgery, University Hospital Lausanne (CHUV), receives 175,000 Swiss francs for the project entitled:

Epigenetic aberrations in low grade glioma, identification of novel therapeutic targets and biomarkers for response to treatment

Epigenetic alterations denote important mechanisms in neoplastic transformation and malignant progression of cancer. Aberrant CpG methylation, an epigenetic modification, has been identified as underlying cause for deregulated expression of genes, but also other regulatory elements including mircoRNAs. This affects diverse cancer relevant pathways leading to activation of oncogenic pathways such as the Wnt pathway, mediated by silencing of Wnt antagonists, or by inactivation of tumor suppressing pathways, including DNA repair. Most interestingly, some of these epigenetic alterations can be converted into the “Achilles heel” of the affected tumors upon treatment with certain classes of anti-cancer agents as we have shown previously for GBM with a methylated MGMT gene that particularly benefit from treatment with the alkylating agent temozolomide.

At present little is known about specific epigenetic alterations and their clinical relevance in low grade glioma (LGG). However, recent reports suggest that most LGG may exhibit a methylator phenotype that displays a high proportion of aberrantly methylated genes of a particular pattern. Curiously, this methylator phenotype is associated with mutation of the IDH1 or IDH2 genes encoding metabolic enzymes. These observations suggest that epigenetic alterations are key events in the development of LGG. Hence, in order to understand underlying molecular mechanisms for successful treatment of LGG, they need to be characterized for genome-wide aberrant DNA methylation and respective associations with clinical parameters including response to therapy. The ultimate goal is to identify novel therapeutic opportunities by rendering epigenetically silenced pathways exploitable for individualized therapy as they sensitize to specific drugs.

Here we propose to determine the DNA methylome as part of an integrated project of multi-dimensional molecular and clinical characterization of LGG of patients treated within a phase III randomized clinical trial (EORTC 22033-26033). The overall hypothesis is that genome wide high resolution CpG methylation profiles in association with high quality clinical data will uncover novel targets for therapy, and biomarkers for prediction of treatment resistance. In order to establish an “unbiased” genome-wide DNA methylome we use MBD2-sequencing (MBD2-seq) for global mapping of methylation in a set of 90 frozen LGG samples from the trial.

The analyses will be extended to FFPE samples that are available for most patients. High resolution CpG methylation mapping of formalin fixed paraffin embedded (FFPE) GBM will be established using the Infinium 450K methylation chip with a novel, FFPE adapted protocol. The 450K Infinium Methylation-BeadChip offers coverage of over 450,000 methylation sites. The combination of two distinct technologies will improve the identification of “true” DNA methylation. Subsequent analyses will comprise unsupervised analyses to identify overall methylation patterns and discovery of new molecular features. In a second strategy we will map aberrantly methylated genes to pathways using gene ontology to identify epigenetically deregulated pathways. Third we will interrogate candidate genes that are key in cancer relevant pathways such as DNA repair, and apoptosis. Fourth, these efforts will be greatly enhanced by correlating the methylome with gene expression and copy number variation data

becoming available for the same samples through associated projects. Functional assays of candidate genes or pathways will be performed using glioma cell lines and sphere lines (tumor stem cell features) *in vitro* and *in vivo* to evaluate the potential for druggability.

Coordinated sample preparation and distribution, and testing of molecular biomarkers relevant for overall translational research in this study will be organized and supported through this project.