SWISS BRIDGE

INVEST IN CANCER RESEARCH WORLDWIDE

SWISS BRIDGE Award for Cancer Research 2016

Summaries of the four supported research projects

Jan Cools, PhD, Group leader at VIB - KU Leuven, Center for Cancer Biology, Leuven, Belgium, receives 250 000 Swiss francs for the project entitled:

Cooperation of oncogenic events in T-cell acute lymphoblastic leukemia

Summary

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive malignancy of immature thymocytes and is one of the rare cancers (incidence in Europe: 1.28/100,000). Treatment strategies have significantly improved over the last 50 years, and long-term survival for pediatric T-ALL patients is now over 80%. Older patients, however, and patients who relapse have much worse prognosis for survival. In addition, current treatment is based on combination chemotherapy, which is associated with many short term and long term toxic side effects. Therefore, there is a strong need to improve therapy in the older patients and reduce the toxicity in the younger patients. Understanding the biology of T-ALL may identify new targets for therapy and open the way for the development of new drugs.

Central to the pathogenesis of T-ALL is the accumulation of multiple genomic lesions, including activating NOTCH1 mutations and chromosomal rearrangements leading to the aberrant overexpression of TAL, TLX, HOXA or NKX transcription factor family members. In addition to direct deregulation of transcription factor expression, also mutations in epigenetic regulators have been frequently found in T-ALL.

My group has mainly focused on the characterization of mutant tyrosine kinase pathways in TALL. We identified ABL1 fusion kinases (NUP214-ABL1 and EML1-ABL1) in 6% of T-ALL cases and characterized these as constitutively activated tyrosine kinases that are sensitive to the kinase inhibitor imatinib. In recent studies, we have contributed to the identification and characterization of mutations in JAK1, JAK3 and the interleukin-7 receptor in 23% of T-ALL cases, which result in constitutive activation of JAK/STAT signaling downstream of cytokine receptors. Interestingly, the NUP214-ABL1 fusion kinase is always associated with TLX1 or TLX3 overexpression, and JAK3 mutations frequently co-occur with HOXA9 overexpression and with loss-of-function mutations in epigenetic regulators including EZH2, SUZ12 and WT1. These are highly significant associations that occur much more frequent than expected by chance. Furthermore, we have developed novel mouse models for T-ALL to test the possible cooperation of these oncogenes, and we have confirmed a functional cooperation between NUP214-ABL1 and TLX1 and between JAK3 mutants and HOXA9. The mechanism of cooperation between oncogenic kinases and transcription/epigenetic factors remains, however, unclear.

The overarching goal of this project is to determine the mechanism of cooperation between oncogenic tyrosine kinase mutants and oncogenic transcription/epigenetic factors and to use this information for the development of novel treatment strategies.

Sara Christina Meyer, MD, PhD, Division of Hematology and Department of Biomedicine, University Hospital Basel, Switzerland, receives 250 000 Swiss francs for the project entitled:

Dual targeting of oncogenic JAK2 and ERK1/2 signaling as novel therapeutic approach in myeloproliferative neoplasms

Summary

Myeloproliferative neoplasms (MPN) are chronic hematologic malignancies with excessive proliferation of mature myeloid cells and potential transformation to acute myeloid leukemia. Hematopoietic stem cell transplantation is the only curative therapy, but is limited to a subset of patients. Novel therapeutic options based on a detailed molecular understanding are needed. MPN are characterized by somatic mutations inducing hyperactive JAK2 signaling. JAK2 is a tyrosine kinase associated with hematopoietic cytokine receptors, which activates STAT-, phosphoinositide-3 kinase (PI3K) and mitogen activated protein kinase (MAPK) signaling pathways. The MAPK pathway includes the sequential kinases RAF, MEK1/2 and ERK1/2. Activation of the MAPK pathway in MPN is not well characterized, and the significance of ERK1 and ERK2 (ERK1/2), the distal kinases in the MAPK cascade, has not been clarified. Investigations of the MAPK pathway and specifically ERK1/2 are needed to develop improved therapeutic approaches. JAK2 inhibitors have been developed due to the central role of JAK2 for oncogenic signaling in MPN, but fail to induce molecular remission and elicit resistance. I studied a new, highly effective mode to target JAK2 (type II JAK inhibition), which reduces the mutant clone and abrogates resistance to conventional (type I) JAK inhibitors. However, the MAPK pathway remained activated in MPN in vivo despite JAK2 inhibition. This suggests JAK2-independent signaling via the MAPK pathway limiting efficacy of JAK2 inhibitor therapy. I am studying the mechanisms of MAPK pathway activation and dual targeting of JAK2 and the MAPK pathway in MPN and other tyrosine kinase mutant hematologic malignancies supported by an SNF Ambizione-SCORE grant and Swiss Cancer League. We are targeting MAPK signaling at the level of MEK1/2, as MEK inhibitors have shown clinical benefit in solid cancers. We find that dual inhibition of JAK2 and MEK1/2 is superior to JAK2 inhibitor monotherapy in preclinical MPN models. This highlights the relevance of the MAPK pathway and calls for further studies on MAPK signaling in MPN adressing also the role of ERK1/2, downstream kinases involved in hematopoiesis. My application for the SWISS BRIDGE Award 2016 outlines these further studies on significance and therapeutic potential of targeting ERK1/2 in MPN. We will investigate the role of ERK1/2 for MPN pathogenesis and will evaluate dual targeting of JAK2 and ERK1/2, as ERK could be a favorable therapeutic target. We will employ genetic and pharmacologic targeting of ERK1/2 in MPN cells, patient samples and murine models. We hypothesize that ERK1/2 loss will delay MPN disease development. We anticipate ERK1/2 as a superior therapeutic target in the MAPK pathway due to its implication in hematopoiesis and its more distal position in the pathway rendering compensatory feedback less probable than for inhibition of the more proximal kinases MEK1/2 or RAF. We aim to validate dual targeting of JAK2 and ERK1/2 as a novel therapeutic approach in preclinical MPN models as rational basis for designing first clinical studies with dual JAK2 and ERK1/2 inhibition in MPN.

Professor Christian Mosimann, PhD, Institute of Molecular Life Sciences, University of Zürich, Switzerland, receives 250 000 Swiss francs for the project entitled:

Regulatory feedback and secretory pathway disruption in chordoma

Summary

Chordoma is a rare, slow-growing tumor that arises from remnant cells of the notochord, a collagen-secreting embryonic structure that normally regresses before birth. Treatment remains difficult due to the delicate surgical removal and radiation/chemo resistance of chordoma.
We aim to clarify the unknown tumorigenic mechanisms in chordoma and other secretory cell-based RTK/Ras-dependent cancers towards uncovering novel therapeutic approaches using the first animal model for chordoma in zebrafish (Danio rerio).
Chordoma genomes predominantly feature deletions and amplifications, including of the T/Brachyury gene and of several RTK loci; the causative impact of these mutations remains undetermined. Brachyury is a developmental T-box transcription factor that drives mesodermal cell fates and EMT. Its expression is controlled by an incompletely charted program that includes feedback loops with RTK/Ras-relayed pathways.
To study chordoma in vivo, we leverage our long-standing transgenics expertise in our recently established first chordoma animal model in zebrafish. The zebrafish embryo provides a potent model for chordoma formation: zebrafish chordomas rapidly form within 3-5 days in developing notochord cells that mimic RTK pathway activation by expressing oncogenic Ras. The resulting tumors share extensive histo-pathological features with human chordoma, providing a potent platform for genetic and chemical compound testing.
Our preliminary work has revealed Brachyury-bound candidate enhancers around the frequently amplified 4q12 RTK genes KDR, KIT, and PDGFRA. Nonetheless, Brachyury misexpression alone is insufficient to drive significant notochord transformation in our model, underlining the requirement for additional transforming events in chordoma. By electron microscopy and transcriptome analysis, we have further uncovered hyperactivation of secretory activity and endoplasmic reticulum (ER) accumulation in Ras-transformed notochord sheath cells. We hypothesize that Brachyury amplification in chordoma coincides with amplification or constitutive activation of RTK genes and secretory pathways to sustain a tumor-maintaining positive feedback loop. Our preliminary data suggests that increased ER activity downstream of RTK/Ras-Brachyury activation could support the rapid cell cycle progression and loss of tissue integrity in chordoma and in tumors of secretory cell types. Breaking this feedback loop and interfering with increased secretory pathway activity could provide a potent therapeutic opportunity to target chordoma and possibly any of the increasingly recognized Ras/Brachyury-expressing rare tumor types.

Pieter Van Vlierberghe, PhD, Center For Medical Genetics Ghent, Ghent University Hospital and Cancer Research Institute Ghent, Belgium, receives 250 000 Swiss francs for the project entitled:

Understanding sensitivity towards LSD1 inhibition in T-cell acute lymphoblastic leukemia

Summary

T-cell acute lymphoblastic leukemias (T-ALLs) are rare aggressive hematologic tumors resulting from the malignant transformation of T-cell progenitors. The prognosis of T-ALL has gradually improved with the introduction of intensified chemotherapy. However, the outcome of T-ALL patients with primary resistant or relapsed leukemia remains extremely poor. Therefore, current research efforts are focused on the development of more effective and less toxic anti-leukemic drugs, which will likely require an improved understanding of the molecular biology of chemotherapy resistant residual tumor cells that eventually drive disease recurrence.
Recent studies have shown the importance of epigenetic changes during cancer etiology and have shed light on the oncogenic evolution of cancer stem and progenitor cells. Therefore, epigenetic therapies have been proposed as a novel strategy to target the therapy-resistant cancer stem cells. In that context, the histone demethylase LSD1 has recently emerged as an attractive therapeutic target for the treatment of various human cancer types and different potent LSD1 inhibitors are currently being tested in clinical trials. Nevertheless, the molecular mechanisms that drive susceptibility towards LSD1 inhibition remain largely unknown. In addition, there are currently no biomarkers available to select cancer patients that might benefit from this particular epigenetic therapy.
Recently, we demonstrated that up to 30% of human T-ALL cell lines are sensitive to LSD1 inhibition and strongly depend on the function of LSD1 for their leukemic survival. Given that sensitive T-ALL cell lines covered a wide range of tumor immunophenotypes and were not restricted to one particular genetic T-ALL subtype, we believe that LSD1 inhibition could serve as novel therapeutic target in a broad panel of human T-cell leukemias. Given this, the ultimate goals of this research project are 1) to unravel the molecular mechanisms that drive LSD1 sensitivity, 2) identify predictive biomarkers for LSD1 inhibitor sensitivity and 3) further evaluate the potential use of LSD1 inhibition as a novel therapeutic approach for the treatment of this rare, but aggressive subtype of human cancer.