BASIC INFORMATION ON SUB-PROJECT

NAME OF PROGRAMME/FUND	Scholarship Fund - Sciex NMS[ch]
RESEARCH FIELD AND OTHER RESEARCH FIELDS INVOLVED (if applicable)	Medical Sciences
TITLE OF THE SUB-PROJECT	Mechanisms of BCR/ABL leukaemogenesis (PhALL)
REGION OF THE CZECH REPUBLIC (according to the location of the home institution)	Prague
GRANT AMOUNT SPENT	93 706,15 CHF
INTERMEDIATE BODY	Swissuniversities
HOME INSTITUTION	Charles University, 2nd School of Medicine Department of Paediatric Haematology and Oncology
HOST INSTITUTION	University Childrens Hospital Zurich Division of pediatric Oncology /Bone Marrow Tranplantation Unit
NAME OF THE FELLOW	Lucie Slámová

ABSTRACT OF THE SUB-PROJECT	Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy. A subgroup with high risk disease is characterised by the presence of translocation t(9;22), which results in the derivative chromosome 22 (Ph chromosome) with BCR/ABL fusion gene. Recent studies have revealed that most Ph+ ALLs carry deletions of IKZF1 gene, a master regulator of B cell ontogenesis. The laboratories in Prague have rare biological material stored from patients with BCR/ABL-positive leukaemia. The laboratory in Zurich has established a representative preclinical research platform using xenotransplant model generating human leukaemia with stable immunophenotype in immunodeficient mice. Our pilot transplantations for this project show consistent engraftment of Ph+ ALL cells. Recently we published data indicating presence of haematopoietic stem or progenitor cell (HSC) that has acquired the BCR/ABL lesion but is distinct from the ALL population. We aim to characterise this residual BCR/ABL-positive subpopulation and understand to which extent this could represent a preleukaemic HSC. Cells from diagnostic pre-treatment bone marrow samples will be sorted into three compartments (lymphoblastic cells, myeloid cells and immature HSCs). A portion of the sorted cells will be used for molecular characterisation (determination of molecular profile of the genetic lesions using SNP arrays and PCRs for characteristic lesions including IKZF1 and comparison of genetic markers in ALL subpopulations and in non-lymphoblastic cells from Ph+ ALL patients) and the second part will be sorted directly into supporting NSG bone marrow and used immediately for xenotransplantation to validate the populations functionally. Moreover, we aim to analyse paired diagnosis vs. relapse samples in order to characterise changes secondary to the BCR/ABL fusion (IKZF1 or other lymphoid regulatory genes). This will enable us to determine, whether these secondary lesions originate in different subclones and possibly show that these lesions are downstream of the BCR/ABL fusion.

MAIN RESULTS	Besides cases with Phildelphia positive ALL which display a significant myeloid population that is detectable at diagnosis and/or during the initial phase of treatment, we identified a specific new subgroup of patients with acute mixed phenotype leukemia, T/myelo and new subset of patient with lineage-switch leukaemia (swALL). While improving the xenograft model to dissect subpopulations in Philadelphia positive leukemia, we have focused our efforts on this new subtype of ALL that switches a subpopulation from a lymphoid phenytype to a myelo-monocytic phenotype under chemotherapy and are using the xenograft system to functionally defined the compartment of cells that appears to transdifferentiate. We have now identified 15 individual patients (4% of B precurors ALL cases) that display a residual population with monocytic features (marked increase in CD33 and CD14, decrease in CD34 and CD19) during the first month of chemotherapy when glucocorticoids playng the main role. This subpopulation derives from the same leukemic clone, because the same ALL specific Ig-TCR clonal rearrangement pattern was retrieved from sorted monocytoid cells from these patients. Remarkably, in most cases these patients had unfavorable risk stratification features or relapsed, suggesting that this phenotype is associated with drug resistance. In particular one patient has relapsed with an AML bearing the same Ig/TCR rearrangement than the initial diagnostic ALL sample, suggesting the possibility of a subclone or clonal evoluation towards a myeloid phenotype. Interestingly, two cases with Philadelphia positive ALL had these switch phenotype. The mechanisms of action involved appear to be cell autonomous, because this lineage switch phenotype was also triggered in xenografted swALL samples in vitro and in vivo after treatment with glucocorticoids. We did not identified common genetic alteration expect of p16 deletion (4/13) and deletion/alteration of IKZF1 gene (5/12). Preliminary data indicate that this phenomenon could be associated with epigenetic modifications of the master regulator of hematopoiesis CEBPA in this subtype of ALL. Collectively, our data suggests that swALL represent a new subtype of BCP ALL that biomarkers can be defined to identify these cases at diagnosis or very early into treatment. Publication: Leukemia. 2014 Mar;28(3):609-20. doi: 10.1038/leu.2013.354. Epub 2013 Nov 25. CD2-positive B-cell precursor acute lymphoblastic leukemia with an early switch to the monocytic lineage. Slamova L1, Starkova J1, Fronkova E1, Zaliova M1, Reznickova L1, van Delft FW2, Vodickova E3, Volejnikova J1, Zemanova Z4, Polgarova K1, Cario G5, Figueroa M6, Kalina T1, Fiser K1, Bourquin JP7, Bornhauser B7, Dworzak M8, Zuna J1, Trka J1, Stary J1, Hrusak O1, Mejstrikova E1.

DATE OF REALISATION OF THE FELLOWSHIP	1.9.2010 - 29.2.2012
MORE INFORMATION ON THE PROGRAMME	**www.sciex.ch**