ImmunoTools *special* Award 2021

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Fetal liver-derived hematopoietic cell lines as novel tool to study acute myeloid leukemia

Acute myeloid leukemia (AML) is an aggressive malignant disease characterized by rapid progression and poor survival rates. Although great effort has been put into the development of novel therapeutic approaches the clinical outcome did not considerably improve over the past decades. While the five-year survival of younger patients ranges between 35 and 40%, for the majority of patients, which are over 60 years old, five-year survival drops to only 15%. One protein often found overexpressed or constitutively activated correlating with adverse disease outcome in AML patients is the signal transducer and activator of transcription 3 (STAT3). STAT3 exists in two isoforms that are obtained by alternative splicing: the full-length isoform STAT3α and the C-terminally truncated isoform STAT3β. Initially described as the dominant negative form to STAT3α the truncated version STAT3β turned out to be also capable of inducing transcription of target genes independently of the full-length isoform STAT3α. Recently, the truncated isoform STAT3β was identified as a novel tumor suppressor and potential prognostic marker in AML (Aigner et al. 2019). Although STAT3β was shown to play a role during differentiation and cellular mobilization of myeloid cells - potentially explaining its tumor suppressive properties - the exact molecular mechanisms in leukemic cells remained up to now elusive.

In my PhD project, I am using a combination of various *in vitro* assays and AML *in vivo* models, to investigate the STAT3 isoform-specific impact on cellular mechanisms

shaping AML development and progression. As basis of my project, I generated murine AML-blast like cell lines that either express solely STAT3α or STAT3β. To do so, murine fetal liver-derived hematopoietic stem cells were oncogenically transformed to AML-blast like cells. As an alternative approach, we generated murine fetal liver-derived hematopoietic progenitor cell lines, which was previously described for bone marrow cells (Doma et al. 2021). With this novel tool we want to investigate the impact of STAT3 isoforms on differentiation which also plays a crucial role in leukemia.

Since the culturing conditions of those cell lines require supplementation with rm IL-3, rm IL-6 and rm SCF, the cytokines and antibodies from **ImmunoTools** would be perfectly suited to support my research project. Furthermore, several cytokines could be used to induce differentiation (rm IL-7, rm TPO, rm GM-SCF) *in vitro*, while murine antibodies would be helpful to determine the differentiation potential of the cells (CD3e, CD19, erythroid cells, CD4, CD44) using flow cytometry. The cytokines and antibodies provided by **ImmunoTools** would be a great opportunity for us to characterize the above-mentioned hematopoietic progenitor cell lines and use them as a new tool in our laboratory. On the one hand we can hereby reduce the number of animals used for fetal liver isolation, and on the other hand this enables us to generate murine AML cell lines lacking STAT3α as absence of Stat3α in mice is perinatally lethal.

We would hereby provide novel insights into the biology of AML development, and the role of STAT3 isoforms therein. Considering the currently investigated STAT3 inhibitors for cancer therapy, understanding the mechanism behind the tumor suppressive function of STAT3β in AML could have significant translational impact. We hope you consider our research goals as adequate and are looking forward to your response.

ImmunoTools *special* AWARD for **Sophie Edtmayer** includes 10 reagents

PE - conjugated anti-mouse CD3e, CD4, CD19, CD44, Erythroid cells

recombinant mouse rm IL-3, rm IL-6, rm IL-7, rm TPO, rm GM-SCF

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