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MEETING ABSTRACT

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The balance between STAT3 isoforms as essential feature in acute myeloid leukemia

Stefanie WEISS[1,*], Anja HOLZER[2], Sophie EDTMAYER[1], Kerstin FIEDLER[1], Bernhard ZDÁRSKY[1], Agnieszka WITALISZ-SIEPRACKA[1], Dagmar STOIBER-SAKAGUCHI[1]

[1] *Division of Pharmacology, Department of Pharmacology, Physiology and Microbiology, Karl Landsteiner University of Health Sciences, Krems an der Donau, Austria;* [2] *Division of Molecular Oncology and Hematology, Department of General and Translational Oncology and Hematology, Karl Landsteiner University of Health Sciences, Krems an der Donau, Austria*

Background: Dysregulation of the JAK/STAT pathway and over-expression of the signal transducer and activator of transcription 3 (STAT3) is frequently found in hematologic malignancies. Constitutively activated STAT3 is associated with significantly poorer outcomes. On account of this, STAT3 became an attractive therapeutic target. However, until now these drugs have not yielded the intended effects. This phenomenon might be related to the expression ratio of the two alternatively spliced isoforms: the full-length isoform STAT3α and the C-terminally truncated STAT3β. Recently, STAT3β was shown to act as a tumor suppressor in acute myeloid leukemia (AML). In line, the *STAT3β/α* mRNA ratio in leukemic blasts of patients with bad prognosis was significantly lower than in those with good prognosis.In the light of these previous findings, the pharmacological induction of a higher STAT3β/α ratio could be a novel therapeutic option in AML.

Methods: To examine the efficiency of candidate drugs in affecting the STAT3 isoform ratio in leukemic cells, we perform *in vitro* assays such as real-time quantitative PCR and western blot. To check their migration behavior *in vitro* we use Transwell Migration Assays. In addition, we plan to test the anti-leukemic drug activity *in vivo*, using an MLL-AF9-induced mouse model and xenograft models.

Results: We observed that STAT3 isoform expression on protein and mRNA levels can be influenced by drug treatment in different human and murine AML cell lines. Therefore, we want to further analyze the underlying mechanism of these drugs influencing STAT3 isoform expression. Interestingly, we could identify the common antimalaria drug atovaquone as a potentially attractive candidate. The effect of an increased STAT3β/α ratio is paralleled by the anti-leukemic activity of atovaquone. Furthermore, we plan to address the anti-leukemic effect of atovaquone *in vivo*. Other antimalaria drugs and a structure analogue of atovaquone had no impact on the expression of the two alternatively spliced STAT3 isoforms.

Discussion: We have demonstrated a novel property of the anti-malaria drug atovaquone. It positively affects the STAT3β/α ratio in AML cell lines, which could be potentially of therapeutic relevance in AML.

Keywords: acute myeloid leukemia – STAT3 – atovaquone

*Corresponding author e-mail: *stefanie.weiss@kl.ac.at*