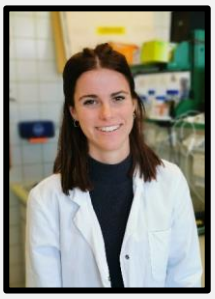
ImmunoTools *special* Award 2023



Julia List, PhD-student

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Alterations in the INK4a/ARF Pathways allow the Establishment of a preclinical NK cell leukemia Mouse Model

The INK4a/ARF locus encodes two distinct tumor suppressors involved in two different pathways: p16INK4a blocks cell-cycle progression by inhibiting phosphorylation of the retinoblastoma protein, while ARF (p14ARF in humans and p19ARF in mice) promotes the functions of p53. Both pathways are important in the cell cycle regulation and involved in processes of senescence and apoptosis. Loss or epigenetic dysregulation of the INK4a/ARF locus or other players of these pathways is observed in several types of cancer, in particularly leukemias and lymphomas. We are investigating the effect of the INK4a/ARF loss on NK cells – NK cell proliferation, NK cell senescence and their leukemic transformation.

We observed that both INK4a and ARF are upregulated in senescent NK cells and that their concomitant loss allows NK cells to escape from the senescence state and shows a proliferative advantage. This allows the establishment of stable mouse NK cell lines. We further study the role of the INK4a/ARF locus in the development and progression of NK cell malignancies. NK cell malignancies are among the most aggressive lymphoid neoplasms and have limited treatment options with a median survival rate of 2 months. An adequate mouse model of NK cell leukemia is highly needed for a better understanding of the mechanisms of tumorigenesis and an exploration of possible new therapeutic strategies.

Our data pinpoint a relationship between the loss of the INK4a/ARF gene within NK cells and their malignant transformation. By making use of this oncogenic potential of NK cells isolated from INK4a/ARF knockout mice, we established a transplantable NK cell leukemia mouse model.

To further show the patient-relevance of our pre-clinical model, we are planning to establish patient-derived xenograft models with human NK cell leukemia patient material. This NK cell neoplasm patient has a complete loss of the INK4a/ARF locus, indicating additionally the relevance of this gene in this aggressive disease. To analyze the leukemic patient material from the xenografts, the selected reagents from ImmunoTools would be extremely helpful to advance our research, contributing to a better understanding of the complexity of leukemic NK cells. We would use the selected

ImmunoTools antibodies for flow cytometry (CD56, CD3, CD16, CD57, CD69, IFN-γ) to get a better understanding of the transformed human NK cells. We also plan to check the human leukemic NK cells from the Xenografts for their cytokine dependency and would therefor use your human cytokines (IL-2 and IL15).

We aim to use this patient-relevant pre-clinical NK cell leukemia mouse model, the generated leukemic mouse NK cell lines and the patient-derived xenograft model to further study the mechanism of transformation, the route of disease manifestation and progression and to identify novel therapeutic vulnerabilities for this disease.

The work will also expand our understanding of NK cell ageing and senescence and its functional consequences and may help to optimize future treatments by preventing senescence-induced NK cell dysfunction in the context of NK cell immunotherapy.

ImmunoTools *special* AWARD for **Julia List** includes 8 reagents

FITC - conjugated anti-human CD16, CD57, CD69

PE - conjugated anti-human CD3, IFN-gamma

APC - conjugated anti-human CD56

recombinant rh IL-2, rh IL-15

DETAILS more AWARDS