

Julia Feichtinger

Gottfried Schatz Research Center for Cell Signaling, Metabolism & Aging (Cell Biology, Histology and Embryology), Medical University of Graz



Project Titel: The immunomodulatory effects of the NR4A1/p53 axis in diffuse large B cell lymphoma

Background:

Diffuse large B cell lymphoma (DLBCL) is the predominant lymphoid malignancy in the western world. While immune checkpoint blockade therapy is in clinical practice for a number of cancer types, the response rates for B cell lymphomas remain disappointingly low. Importantly, immune evasive mechanisms are still poorly investigated in B cell lymphomas, which has impeded the progress in developing new therapeutic approaches targeting the lymphoma immune landscape. This *in-silico* project aims to address this gap by investigating the immunomodulatory effects of the NR4A1/p53 axis, two pivotal transcription factors and tumour suppressors.

Hypothesis and Objectives:

Our preliminary data strongly suggests that NR4A1 and p53 build a functional axis to orchestrate immune evasive mechanisms in DLBCL. We therefore hypothesize that the NR4A1/p53 status results in distinct expression patterns of immunomodulatory factors (such as coinhibitory immune checkpoint receptors/ligands, MHC and cytokines), which in turn influences the anti-tumour response. Furthermore, we anticipate that the NR4A1/p53 status holds significant clinical relevance in human DLBCL. This project is part of a consortium initiative with objectives that include the investigation of mouse models with Nr4a1 and/or p53 knockout and the exploration of treatment options. Additionally, the aim is to translate findings of the Nr4a1/p53 axis in mice into a clinical setting using the GRAZ lymphoma cohort.

Methodology:

The PhD will focus on the *in-silico* part of the consortium initiative by leveraging bioinformatics methods, data analysis and mining techniques. The analysis of transcriptomics data (qPROseq, (single-cell) RNA-seq) will serve as the foundation for investigating the expression patterns of immunomodulatory factors, anti-tumour response and tumour microenvironment. To explore the clinical relevance of the NR4A1/p53 axis and inter-patient heterogeneity, a comprehensively annotated DLBCL dataset will be processed and analyzed. This dataset includes multiple read-outs such as the NR4A1/p53 status, mutations, expression data of immunomodulatory factors, composition of tumour-infiltrating immune cells, *ex vivo* response rates and clinical parameters.

References:

Fechter K, Feichtinger J, Prochazka K, Unterluggauer JJ, Pansy K, Steinbauer E, Pichler M, Haybaeck J, Prokesch A, Greinix HT, Beham-Schmid C, Neumeister P, Thallinger GG, Deutsch AJA: **Cytoplasmic location of NR4A1 in aggressive lymphomas is associated with a favourable cancer specific survival.** *Sci Rep* 2018, **8**:14528.

Deutsch AJA, Rinner B, Wenzl K, Pichler M, Troppan K, Steinbauer E, Schwarzenbacher D, Reitter S, Feichtinger J, Tierling S, Prokesch A, Scheideler M, Krogdram A, Thallinger GG, Schaider H, Beham-Schmid C, Neumeister P: **NR4A1-mediated apoptosis suppresses lymphomagenesis and is associated with a favorable cancer-specific survival in patients with aggressive B-cell lymphomas.** *Blood* 2014, **123**:2367-2377.

Pansy K, Fechter K, Wenzl K, Arra A, Novak JP, Szmyra M, Haingartner S, Ramsay AG, Novak AJ, Greinix HT, Beham-Schmid C, Neumeister P, Deutsch AJA: **Loss of Nr4a1 Causes an Elevated Expression of Co-Inhibitory Receptor: Ligand Axes and Results in a Diminished T Cell-Mediated Lymphoma Cell Killing in Aggressive Lymphoma.** *Blood* 2022, **140**(Supplement 1):2038-2039.

Pansy K, Uhl B, Krstic J, Szmyra M, Fechter K, Santiso A, Thümingner L, Greinix H, Kargl J, Prochazka K, Feichtinger J, Deutsch A: **Immune regulatory processes of the tumor microenvironment under malignant conditions.** *Int J Mol Sci* 2021, **22**:13311.

Wenzl K, Stokes M, Novak JP, Bock AM, Khan S, Hopper MA, Krull JE, Dropik AR, Walker JS, Sarangi V, Mwangi R, Ortiz M, Stong N, Huang CC, Maurer MJ, Rimsza L, Link BK, Slager SL, Asmann Y, et al.: **Multiomic Analysis Identifies a High-Risk Metabolic and TME Depleted Signature that Predicts Early Clinical Failure in DLBCL.** *medRxiv* 2023:2023.06.07.23290748.