ESOT Transplant Fellowship – Research progress report

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Please report your project/research progress below (also highlighting if you met your proposed goals).

At the start of the fellowship year, we designed an ambitious research plan that was divided in 2 work packages (see overview Figure below). In the first work package, we aimed to describe the post-transplant course of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and establish a predictive model for adverse outcomes. In the second work package, we aimed to gain insight into the mechanism of autoimmune activation of the immune system and investigate its relative importance in kidney transplant rejection.

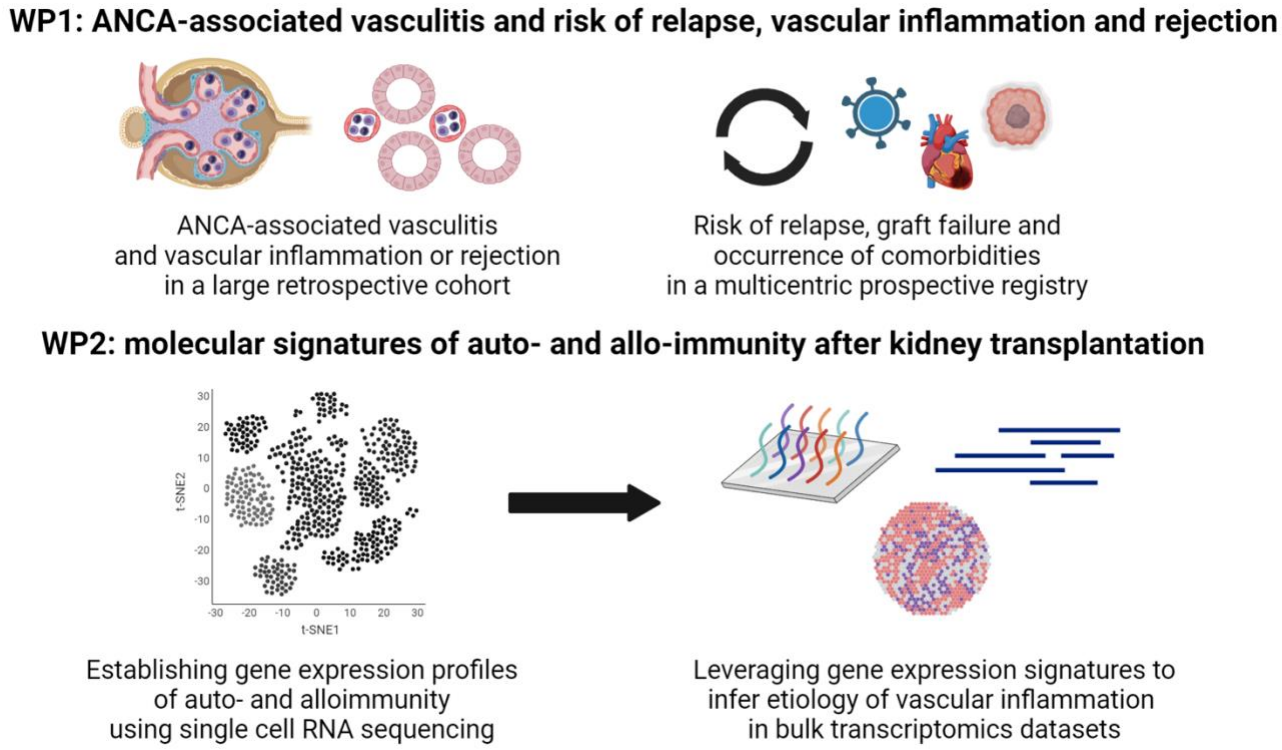

Figure 1. Research plan during ESOT Transplant Fellowship

Work package 1: ANCA-associated vasculitis and risk of relapse, vascular inflammation and rejection

In a retrospective cohort study of transplant recipients from Leuven and Innsbruck, we identified 94 patients with underlying ANCA-associated vasculitis or anti-glomerular basement membrane (GBM) disease. We decided to include the latter disease given the high overlap in presentation and treatment for these patients. We matched these patients in a 1:2 ratio based on recipient age, sex, history of previous transplantation, transplant year and center. Interestingly, we found that patients with ANCA-associated vasculitis or anti-GBM disease had an increased risk for infection (subdistribution hazard ratio [sHR] 1.81, 95% confidence interval [CI] 1.14-2.88) and malignancy (sHR 2.41, 95% CI 1.20-4.83). The manuscript of this work has been finalized and will be submitted to a high-impact Nephrology journal in the coming weeks.

To better understand the risk factors leading to adverse post-transplant outcomes in recipients with crescentic GN, we are now building an international consortium together with prof. Benoît Brilland (University of Angers, France). The AVATAR consortium (ANCA-associated VAsculitis and anti-GBM disease: kidney TransplAnt Results) aims to collect sufficient patient data to examine granular questions such as the association between exposure to pretransplant immunosuppression and infections or malignancies. So far, 20+ centers are willing and interested to join. Having overcome several legal hurdles, we now expect to initiate data collection in Q4 of 2025.

Work package 2: Molecular signatures of auto- and alloimmunity after kidney transplantation

In the second work package, we aim to uncover signatures of autoimmunity to better understand why vascular inflammation occurs after transplantation. It has been proposed that autoimmune triggers may lead to immune-mediated graft injury, but the importance and prevalence of this mechanism is not well understood.

In a first step, we aim to define specific transcriptional features of autoimmunity. We decided to use ANCA-associated vasculitis as a model for autoimmune vascular inflammation and performed single cell RNA sequencing on peripheral blood mononuclear cells (PBMCs) that were collected from patients included in the RAVE trial at different time points (see below). In the past year, we have identified and sequenced 16 samples for this study and performed several preliminary analyses. Interestingly, we observed transcriptomic differences in the immune cells based on the underlying causative antibody, i.e. anti-myeloperoxidase vs. anti-proteinase 3 antibodies. We are now performing more detailed analyses of the immune activation patterns.

In a next step, we will compare these patterns with the transcriptional changes in PBMCs from patients with antibody-mediated rejection (AMR), a stereotypical example of alloimmune induced vascular inflammation. By a comparison of PBMCs in ANCA-associated vasculitis and AMR, we aim to obtain specific signatures of auto- and alloimmunity, respectively. The scRNAseq analysis of PBMCs in AMR has already been

performed in a previous project in the Naesens lab (KU Leuven). These signatures will then be leveraged using bulk transcriptomics on kidney allograft biopsies with vascular inflammation. Specifically, we will analyze biopsies with unexplained vascular inflammation, i.e. in the absence of donor-specific antibodies, to gauge the potential contribution of autoimmunity in the pathogenesis of this phenomenon.

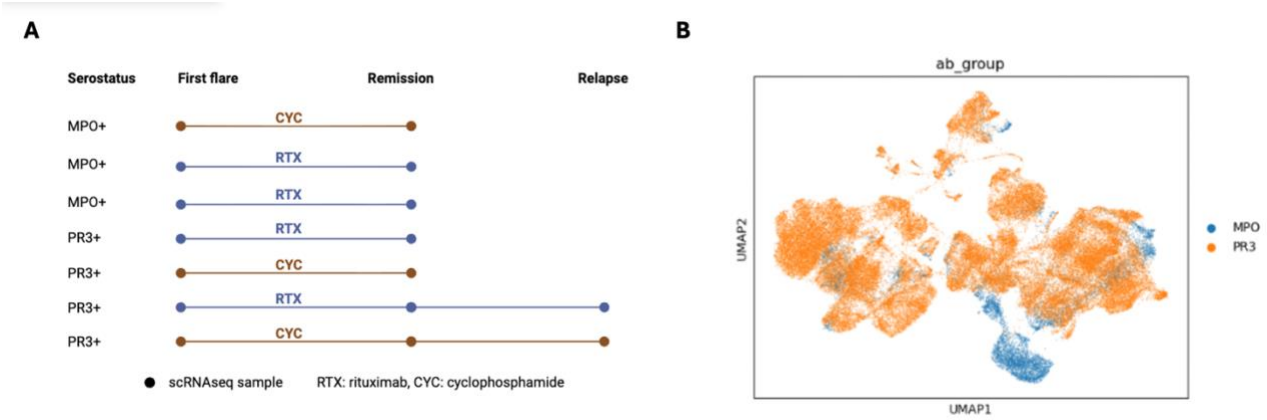

Figure 2 Single-cell RNA sequencing of patients with ANCA-associated vasculitis. A. Study design B. uMAP plot of peripheral blood mononuclear cells of included patients. A distinction is found based on the underlying causative antibody (anti-myeloperoxidase vs. anti-proteinase 3 antibodies).

As can be deducted from this overview, the research plan has not been completed entirely, and several tasks remain. However, it was clear from the onset that the fellowship year would only mark the beginning of a scientific collaboration between Innsbruck and Leuven. During the past year, several preparations have been undertaken to carry these investigations further, such as the involvement of a dedicated bioinformatical team, structured follow-up meetings and establishment of an international consortium.

Innsbruck, 07.10.2025

Signature: Prof. Dr. Andreas Kronbichler PhD