Our main goal is to improve immunotherapy for cancer patients by using translational in vitro and in vivo tumor models, performing correlative analysis of patients treated with immunotherapy and conducting early clinical intervention trials (also see link to Medical Oncology).

One of our research foci is on the role of glycans and glycan-binding receptors in anti-cancer immunity. Glycans can mediate important interactions with immune cells and manipulation of glycans and glycan-binding receptors (lectins) bear a great potential to improve anti-tumor immune reactions. Glycan-mediated interactions in cancer immunology are significantly underexplored and could be used to improve anti-cancer immunity. Our group has studied the interaction between glycans that contain sialic acids (sialoglycans) and their interaction with Siglec receptors on immune cells and have demonstrated that this pathway can be targeted to augment T cell stimulation and tumor control. Current goals include improvement of cancer immunotherapy by modifying glycans in the tumor microenvironment and glycans of cellular products for adoptive cell therapies including genetically modified T cells.

An additional focus of our group is the improvement of immune checkpoint blockade and adoptive cellular therapies by investigating mechanisms and patterns of resistance to these therapies. To this end, we are investigating the tumor microenvironment as well as circulating immune cells in patients undergoing immune checkpoint blockade or adoptive T cell transfer. Identified pathways are further studied in the laboratory for their potential as new targets to improve antitumor immune responses.

**Fig. 1: Upregulation of Siglec-9 ligands in non-small cell lung cancer.**
Squamous cell carcinoma (SCC), adenocarcinoma (AC) or normal lung tissue was stained with Siglec-9-Fc proteins (red) to detect Siglec-9 ligands and merged with cytokeratin staining to identify carcinoma cells. Siglec-9 ligands were found to be more often found in tumor tissue compared to normal tissue (from Stanczak et al., J Clin Invest 2018).
Fig. 2: HLA-F as a ligand for KIR3DS is present in lung cancer patients resistant to PD-1 blockade.
Immunohistochemical staining of lung adenocarcinoma tissue (from Trefny et al., Clin Cancer Res 2019), compared to normal tissue (from Trefny et al., Clin Cancer Res 2019).

Fig. 3: Changes occurring in cancer-associated glycans.
Three main changes can be found in cancer that are regulated by genetic or epigenetic alterations in genes of glycan-modifying enzymes or enzymes involved in carbohydrate biosynthesis. N-glycans show often an increased branching due to increased MGAT5 expression. Another often observed change is the truncation of O-glycans and the exposure of new TACA including the T antigen, Tn antigen and the sialy-Tn antigen (STn). In addition, changes of sialylation of both glycoproteins and glycolipids can be observed. Increased sialylation (hypersialylation) is often observed. The introduction of the non-human sialic acid Neu5Gc can also be observed.

Glc, glucose; Man, mannose; Fuc, fucose; GlcNAc, N-acetyl-glucosamine; Gal, galactose; GalNAc, N-acetyl-galactosamine; N-acetyl-neuraminic acid; Neu5Gc, N-glycosyl-neuraminic acid (from Mantuano et al., J Immunother Cancer 2020).

Selected Publications

Connection to Clinical Practice
Alfred Zippelius, Frank Stenner, Jakob Passweg
Department of Internal Medicine, Division of Oncology and Hematology, University Hospital Basel
Adoptive cell therapy for solid cancers
Adoptive cell therapy with TILs (tumor-infiltrating lymphocytes) for melanoma patients have been developed several years ago at the NIH. Clinical trials have shown high and very encouraging response rates depending on the stage and selection of patients. We have established and expansion protocol for the treatment of melanoma patient refractory to standard immune therapy with checkpoint inhibitors (and BRAF/MEK inhibition in BRAF mutated patients).
Our first planned clinical trial just recently started and will recruit patients. It includes an adapted classical expansion protocol and the application of IL-2 after the adoptive TIL transfer. In addition, we will perform a PD-1 blockade after stopping IL-2 treatment to render the tumor microenvironment more permissive for tumor-attacking T cells. Our program will enable us to expand this treatment option to other tumor types. In addition, we are working to improve the expansion protocols and the specific expansion of tumor-recognizing T cells. Finally, the program will also allow for a direct translation of new genetically modified T cell therapies into early clinical trials.