**Immune modulation in cancer: implications for novel cancer therapies**

Our group is a translational science laboratory in the field of cancer immunology/immunotherapy. We are applying basic research in immunocompetent murine models and tumor specimens from cancer patients. The direct connection to the medical oncology division allows translating preclinical discoveries into early clinical trials.

1. New combinatorial approaches to enhance cancer immunotherapy

A major goal is to develop rational combinatorial approaches that combine the unique ability of immunotherapy to mediate long-term responses and the significant benefits of cytotoxic and targeted anti-cancer therapies. We have discovered that microtubule-depolymerizing agents (MDA) such as maytansins and dolastatins are capable of inducing the full spectrum of maturation changes in dendritic cells (DCs), thereby potentiating the tumor-specific T cell response in vivo. These findings provided novel insights into the therapeutic activity of antibody drug conjugates including T-DT1 (antibody against HER2 coupled to MDA) in eliciting anti-tumor immunity in patients with early breast cancer and a HER2-expressing orthotopic tumor model. Importantly, the combined treatment of T-DM1 with checkpoint inhibitors (antibodies targeting the immune checkpoints CTLA-4 and PD1) induced the rejection of established tumors due to engagement of both innate and adaptive immune mechanisms. This finding led to the initiation of trials in HER2-positive breast cancer that use the combination of T-DM1 and checkpoint inhibitors targeting the PD1/PD-L1 axis.

2. Mechanisms of immune cell dysfunction in cancer

We are interested in dissecting mechanisms underlying T cell dysfunction in cancer patients to improve cancer immunotherapy by identifying synergistic agents and optimizing patient selection. Recent work has elucidated the cumulative expression of inhibitory receptors as a hallmark of dysfunctional T cell tumors and tumor progression, in particular in patients with non-small cell lung cancer. Of note, these inhibitory signals largely impact on the efficacy of treatment-induced immune activation and tumor cell killing. Moreover, changes of the glycocalyx within the tumor microenvironment are investigated and recent work suggests that the cancer-associated upregulation of sialic acid-containing glycans can engage inhibitory receptors such as Siglec-F and significantly inhibit the anti-tumor immune response.

3. Development of anti-cancer strategies in early clinical trials

Our clinical research focus lies on the investigation and development of treatment strategies, targets and delivery platforms in early trials in medical oncology. In collaboration with the Clinical Research Center (CCR) at our division, we have programs ongoing to create a pipeline of agents that can move into the clinic. In translational projects, we aim at defining predictors of therapeutic responses and at understanding the mechanism of treatment responses and resistance. In addition, we define novel tumor antigens by analyzing the autoreactive antibody repertoire. The clinical programs include cancer vaccines, immune modulatory drugs, monoclonal antibodies, and nanoparticles such as immunoliposomes. In collaboration with the Department of Radiology and Nuclear Medicine, a program is centered on radiopeptides against peptide receptors. In addition, to optimally develop novel anti-cancer agents, in particular immunotherapeutics, in vitro organotypic assays are performed to study how these compounds modulate immune effector populations in freshly excised tumor tissue, thus closely mimicking the situation found in cancer patients. This program is performed in collaboration with the Department of Thoracic Surgery, Gynecology and Pathology.