# Cancer Immunology

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## 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 specimen 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. There are now emerging experiences that the latter may turn immune-resistant tumors into tumors sensitive to immune-mediated killing by re-activating pathways within tumors responsible for its recognition and/or killing by immune effector cells. We discovered that microtubule-depolymerizing agents (MDA) such as maytansins and dolastatins are capable of inducing the full spectrum of maturational 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-DM1 (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.

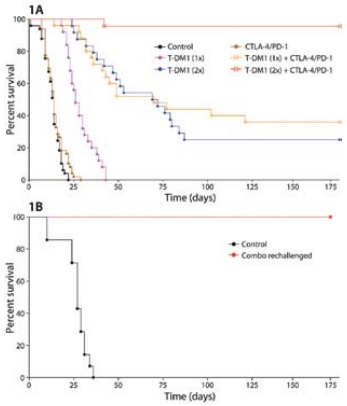


**Fig. 1: (A)** Therapeutic response of the antibody drug conjugate T-DM1 and the combination with checkpoint inhibitors α-CTLA-4/-PD-1 in mice bearing tumors which overexpress human HER2 under the control of the murine mammary tumor virus promoter (Fo5) as a model of huHER2-overexpressing breast cancer. **(B)** Mice which remained tumor-free after combination therapy and control mice were rechallenged in the contralateral mammary gland using cell suspensions from whole Fo5 tumor digests.



**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 cells and tumor progression, in particular in patients with non-small cell lung cancer. Of note, those inhibitory signals largely impact on the efficacy of treatment-induced immune activation and tumor cell killing. Moreover, changes of the glycosylation 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 Siglecs 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 (CCRC) 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.

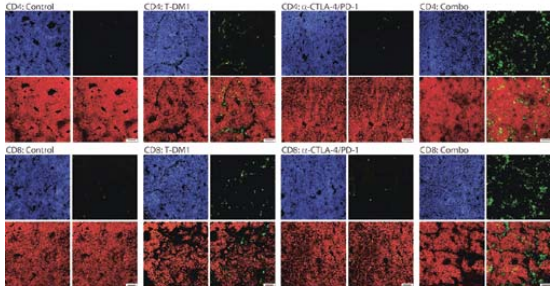


**Fig. 2:** Representative tumor sections treated as indicated were stained for CD4 (upper panel) and CD8 (lower panel) to assess changes of intratumoral immune cell subsets, (blue: DAPI; red: HER2, and green: CD4 or CD8, respectively) (scale bar = 100μm).

## Selected Publications

Müller P, Kreuzaler M, Khan T, Thommen DS, Martin K, Glatz K, Savic S, Harbeck N, Nitz U, Gluz O, *et al.* (2015) Trastuzumab emtansine (T-DM1) renders HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade. Sci. Transl. Med. 7, 315ra188

Schreiner J, Thommen DS, Herzig P, Bacac M, Klein C, Roller A, Belousov A, Levitsky A, Savic S, Moersig W, *et al.* (2015) Expression of inhibitory receptors on intratumoral T cells modulates the activity of a T cell-bispecific antibody targeting folate receptor. Oncoimmunology 5(2), e1062969

Thommen DS, Schreiner J, Müller P, Herzig P, Roller A, Belousov A, Umana P, Pisa P, Klein C, Bacac M, *et al.* (2015) Progression of lung cancer is associated with increased dysfunction of T cells defined by coexpression of multiple inhibitory receptors. Cancer Immunol Res 3(12), 1344–55

Zippelius A, Schreiner J, Herzig P, Müller P. (2015) Induced PD-L1 expression mediates acquired resistance to agonistic anti-CD40 treatment. Cancer Immunol Res 3(3), 236–244

Müller P, Martin K, Theurich S, Schreiner J, Savic S, Terszowski G, Lardinois D, Heinzelmann-Schwarz VA, Schlaak M, Kvasnicka, *et al.* (2014) Microtubule-depolymerizing agents used in antibody-drug conjugates induce antitumor immunity by stimulation of dendritic cells. Cancer Immunol Res 2(8), 741–755

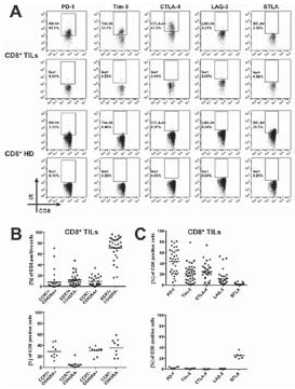


**Fig. 3:** Immune profile of tumor infiltrating CD8⁺ T cells (TILs) from NSCLC patients. **(A)** The expression of the inhibitory receptors PD-1, Tim-3, CTLA-4, LAG-3 and BTLA was determined by flow cytometry on tumor infiltrating CD8⁺ T cells from tumor digestions. **(B)** Distribution of naïve and memory T cell subsets, characterized by CCR7 and CD45RA, in CD8⁺ T cells from lung cancer specimens (TIL) or PBMCs from healthy donors (HD). **(C)** Expression of inhibitory receptors on tumor infiltrating CD8⁺ T cells.