Cancer Immunology

Alfred Zippelius

Department of Biomedicine
Laboratory Cancer Immunology
University of Basel

Christoph Rochlitz

Department of Biomedicine
Medical Oncology
University Hospital Basel

Group Members

Dr. Sandra Kallert*
Dr. Yang Liu
Dr. Gianni Monaco*
Dr. Marina Natoli
Dr. Elham Pishali*
Dr. Vincent Prêtre*
Dr. Marcel Trefny
Dr. Marta Trüb
Dr. Franziska Uhlenbrock*
(Postdocs)

Laura Fernandez Rodriguez
Nicole Kirchhammer
Michal Stanczak*
Sofia Tundo
(PhD Students)

Dr. med. Dominic Schmid
(MD-PhD Student)

Nora Liewen (MD Student)

Adrian Filip
Christine Huynh*
Monika Kaiser*,
Victoria Koch
Caterina Mariani
Eva Neugebauer
Martin Thelen*
Franziska Werner*
(Undergraduate Students)

Dr. Chiara Cianciaruso
Dr. Lucia D'Amico
Dr. Markus Germann
(External Collaborators)

Dr. Abhishek Kashyap*
Prof. Dr. med.Christoph Renner
PD Dr. med. Sacha Rothschild
Prof. Dr. med.Frank Stenner
PD Dr. med. Andreas Wicki*
(Research Associates)

Prof. Dr. med.
Christoph Rochlitz
(Research Group Leader)

Mélanie Buchi
Beatrice Dolder Schlienger
Regina Dönen*
Claudia Gärtner-Pelham
Petra Herzig
Norbert Markuly*
Florian Rosentreter*
Marina Van Ark*
(Technical Staff)

Carmen Vogel
(Administrative Staff)

*left during report period

Immune modulation in cancer: implications for novel cancer therapies

Exploiting the immune system for cancer has become a paradigm-shifting therapeutic arsenal in oncology. Thus, cancer immunotherapy is increasingly considered to be one of the most important advances in the field of medicine following outstanding clinical successes with adoptive T cell therapies or blockade of immune checkpoints (Nobel Price in Medicine, 2018). Yet, therapeutic benefits are currently limited to a minority of treated patients and many patients are either refractory ab initio or develop resistance to such therapies, through yet poorly understood mechanisms. Our research group is a translational science laboratory in cancer immunology and immunotherapy. We are applying basic science research in immunocompetent murine tumor models and primary human tumor specimens and translating our discoveries and knowledge directly into early clinical testing (clinical trial unit including a phase I unit).

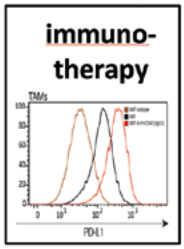
The understanding of cellular and molecular mechanisms of primary and acquired resistance to checkpoint blockade therapy allows for designing novel combination immunotherapy approaches to overcome these resistance mechanisms. In the last years, our research has been dedicated to mechanistically understand the immuno-modulating capabilities of novel anti- cancer therapies in order to pave the way for rationally designed treatment algorithms. We have recently provided insights into the therapeutic activity of immune-modifying chemotherapy that can elicit strong anti-tumor immunity in patients and mouse models. In addition, we showed that resistance to immunotherapy can be successfully overcome by synergistic combinations of immunotherapeutic agents and approaches specifically targeting immune-suppressive pathways. Figure 1 provides an overview with references.

A major barrier for effective cancer immunotherapy is intra-tumoral immune cell exhaustion. A comprehensive understanding of molecular initiators and promoters of T cell exhaustion is key to develop more effective strategies to restore antitumor immunity. Our group is interested in dissecting mechanisms underpinning T and NK cell exhaustion in human cancer patients; accordingly, recent work elucidated the diversity and functional impact of inhibitory T cell receptors expressed in cancer patients. To develop strategies to overcome tumor-induced T cell dysfunction, immunotherapeutic agents endowed with specific immune-activating capacities have been evaluated to induce a functional T cell recovery, thereby enhancing the effector functions in tumor-infiltrating immune cells. Figure 2 provides an overview with references.

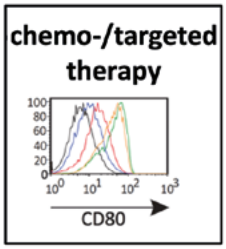
We are currently working on implementing emerging technologies for multidimensional characterisation of the tumor microenvironment. E. g. CODEX is a novel multiplex imaging platform, which is capable of providing information on expression of up to 50 markers from a single tissue slide coupled with spatial coordinates of the cells (Figure 3). It is an excellent tool to study immune cells in their in situ environment. In addition, CyTOF (mass cytometry) is a multi parameter tool allowing for detailed quantification to study the cell subsets in suspension. Therefore, combining CyTOF with CODEX allows for through immune and tumour cell characterisation, also in the samples where material for analysis is limited.

Further work includes clinical research activities embedded into the Immunotherapy network at the Cancer Center of the University hospital Basel (Sebastian, BMC Cancer 2014; Conen, Dermatology 2014; Läubli, J Immunther Cancer 2015; Conen, Dermatology 2015; Kölzer, J immunother Cancer 2016; Koelzer, J Immunother Cancer 2016; Müller, Cancer Immunol Immunother 2016; Läubli, J Immunther Cancer 2017; Ortega, J Immunother Cancer 2018; Läubli, J Immunother Cancer 2018; Läubli, J Immunother Cancer 2018; Ortega, SMW 2019; Läubli, Virchows Arch 2019).

Fig. 1



- *Zippelius, Cancer Immunol Res 2015*
- *Müller, Int J Clin Pharmacol Res 2016*
- *Wieckowski, Lung Cancer 2014*
- *Kashyap, J Immunotherapy of Cancer 2019*
- *Kashyap, PNAS 2020*



- *Müller, Cancer Immunol Res 2014*
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- *Martin, Front Immunol 2015*
- *Läubli, Cancer Immunology Immunotherapy 2018*
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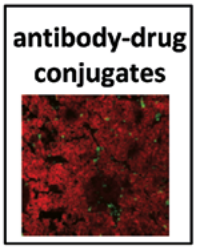

- *Müller, Science Transl Medicine 2015*
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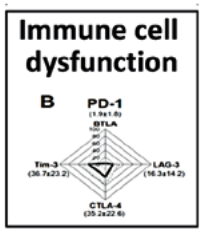
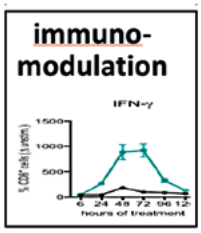
Fig. 2



- *Thommen, Cancer Immunol Res 2015*
- *Thommen, Nat Med 2018*
- *Trefny, Clin Cancer Res 2019*
- *Trefny , Cancer Immunol Immunother 2020*



- *Schreiner, Onco-immunology 2015*
- *Xue, J Natl Cancer Instit 2015*
- *Kallert, Nat Comm 2018*
- *Claus, Science Translat Med 2020*
- *Trüb, J Immuno-therapy of Cancer 2020*

Selected Publications

Trüb M, Uhlenbrock F, Claus C, Herzig P, Thelen M, Karanikas V, Bacac M, Amann M, Albrecht R, Ferrara-Koller C, *et al.* (2020). Fibroblast activation protein-targeted-4-1BB ligand agonist amplifies effector functions of intratumoral T cells in human cancer. J Immunother Cancer. 2020 Jul;8(2):e000238.

Kashyap AS, Schmittnaegel M, Rigamonti N, Pais-Ferreira D, Mueller P, Buchi M, Ooi CH, Kreuzaler M, Hirschmann P, Guichard *et al.* (2020). Optimized anti-angiogenic reprogramming of the tumor microenvironment potentiates CD40 immunotherapy. Proc Natl Acad Sci U S A. 2020 Jan 7;117(1):541–551.

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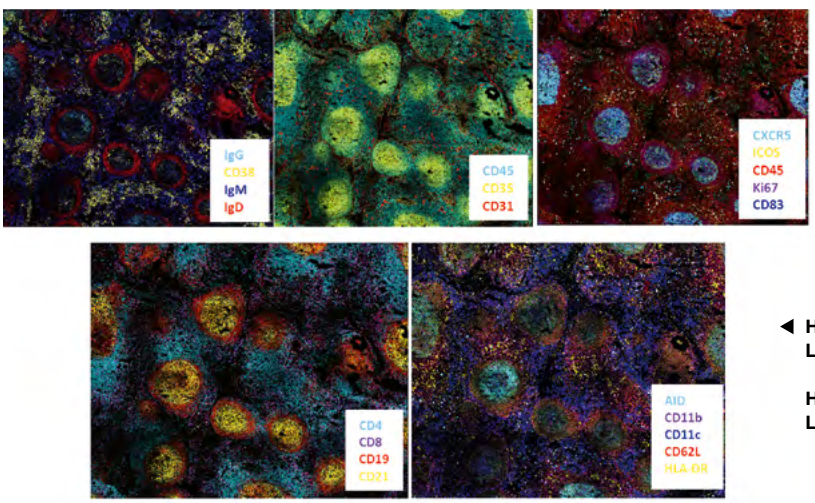
Papachristofilou A, Hipp MM, Klinkhardt U, Früh M, Sebastian M, Weiss C, Pless M, Cathomas R, Hilbe W, Pall *et al.* (2019). Phase Ib evaluation of a self-adjuvanted protamine formulated mRNA-based active cancer immunotherapy, BI1361849 (CV9202), combined with local radiation treatment in patients with stage IV non-small cell lung cancer. J Immunother Cancer. 2019 Feb 8;7(1):38. doi: 10.1186/s40425-019-0520-5.

Thommen DS, Koelzer VH, Herzig P, Roller A. Trefny M, Dimeloe S, Kiialainen A, Hanhart J, Schill C, Hess C, *et al.* (2018). A transcriptionally and functionally distinct PD-1(+) CD8(+) T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade. Nat Med. 2018 Jul;24(7):994–1004.

Fig. 3



◀ **Human Lymph Node**

Human Lung Tumor ▶