Award Winners 2019

1) Prof. Dr. Denis Migliorini, MD (Date of birth: 18.06.1983)

Department of Oncology, Neuro Oncology Division, Center for Translational Research in Onco-Hematology, Geneva University Hospitals and University of Geneva, Switzerland

Short CV:

Nov 2019	**Assistant Professor**, Department of Oncology, University of Geneva
2017-2019	**Postdoctoral Research Fellowship**, Center for Cellular Immunotherapies, University of Pennsylvania, PA (Advisors: Carl H. June, Avery D. Posey)
2014- 2016	**Clinical Fellowship** (Chef de Clinique) Neuro oncology, Department of Oncology, University Hospital of Geneva (Advisor: Pierre-Yves Dietrich)
2011-2014	**Post graduate training** Medical Oncology, University Hospital of Geneva
2008-2011	**Post graduate training** Internal Medicine, University Hospital of Strasbourg
2002-2008	**M.D.**, University of Toulouse Medical School

Project title: **Rational design of inhibitory chimeric antigen receptor (iCAR) to prevent anti CD19 CAR-T cell related neurotoxicity in B-cell malignancies**

Summary:

CD19 directed immunotherapies, including CD19-specific CAR-T cells, have been highly effective for treating B-cell malignancies in patients. However, recent reports have also demonstrated several critical side effects, including a high incidence of neurotoxicity, which in some cases has led to serious morbidity and even death. The pathophysiology of neurotoxicity has remained unclear but has generally been attributed to cytokine release syndrome – i.e. the over-activation of CAR-T cells leading to release of pro-inflammatory cytokines. However, this hypothesis does not explain the higher incidence of neurotoxicity in patients treated with CD19 CAR-T cells compared to CAR-T cells targeting other antigens.
Our data, currently under revision in *Cell*, suggests that CD19 is expressed by a rare non-immune cell type that can be targeted by CD19-specific CAR-T cells and this targeting is directly related to the adverse neurological effects. We tested this hypothesis by analyzing highresolution single-cell RNA-seq maps from the human brain and identified a rare population of brain pericytes expressing CD19 transcripts. Pericytes are a distinct lineage of cells that line the brain vasculature and are crucial for maintaining the integrity of the blood-brain barrier (BBB). We demonstrate CD19 expression in human pericytes using single-cell transcriptome data from several independent datasets as well as protein immunohistochemistry from multiple regions of the human brain. In addition, we perform flow cytometric analysis to identify CD19 expression in CD45- cells from enriched stromal fractions of mouse brain. Finally, we show that in immunodeficient mice, treatment with anti-CD19 CAR-T cells targeting murine CD19, but not those targeting human CD19 or non-modified T cells, results in leakiness of the BBB, suggesting direct attack on brain vasculature and that neurotoxicity can be induced in a B cell-independent mechanism. In summary, we identified a previously unrecognized mechanism for neurotoxicity induced by the administration of anti-CD19 CAR-T cells in humans. These results have significant implications for the use of current CD19-specific CAR-T therapies and ongoing efforts to improve their safety profile. Building on our findings, we wish to perform a follow-up project in which we will:
1) – Perform comprehensive gene expression profiling of human brain pericytes.
2) - Generate novel CAR against targets identified in Aim 1 or optimized, high-affinity versions of targets previously identified in the literature (such as NG2) using phage display library.
3) - Screen and select the most efficient intracellular inhibitory immuno-receptors and test their in vitro and in vivo performance with the ultimate aim of developing a dual-receptor expressing T cell product with cytolytic activity against CD19-expressing B cells, but inhibition of cytotoxicity against CD19+ pericytes.

2) Dr. Lukas Bunse, MD-PhD (Date of birth: 17.06.1988)

Vaccine Development and Cellular Therapies, Neuroimmunology, Neurology Clinic, University Hospital Mannheim, Mannheim, Germany

Short CV:

Since 2019	**Resident in Neurology** at Neurology Clinic, University Hospital Mannheim, University Heidelberg and **Team leader Vaccine Development and Cellular Therapies, Neuroimmunology**, Neurology Clinic, University Hospital Mannheim
2016-2019	**PhD student (Dr. rer. nat.)** at Faculty of Biosciences, University Heidelberg and CCU Neuroimmunology and Brain Tumor Immunology, DKFZ Heidelberg (Advisor: Michael Platten)
2016-2018	**Postdoctoral fellow** at Neurology Clinic, University Hospital Heidelberg, University Heidelberg (Advisor: Wolfgang Wick)
2013-2014	**Research fellow** at Ann Romney Center of Neurologic Diseases, Brigham and Women´s Hospital, Harvard Medical School, Boston, USA (Advisor: Francisco Quintana)
2012-2016	**MD doctoral thesis (Dr. med.)** at DKFZ Heidelberg and Neurology Clinic, University Hospital Heidelberg (Advisor: Michael Platten)
2009-2016	**Medical School** University Heidelberg and Institute of Neurology, University College London (UCL), England

Project title: T cell receptor transgenic cellular therapies targeting shared T helper cell neo-epitopes in brain tumors

Summary:

Adoptive T cell therapy using genetically engineered T cells expressing a chimeric antigen receptor (CAR) against the B cell antigen CD19 has achieved remarkable regressions in leukemia and lymphoma patients. Translation of this cellular concept to solid tumors has proven to be difficult, a major hurdle being the identification of suitable cell surface antigens or tumor-associated antigens (TAAs) as T cell targets that mediate effective tumor-killing without causing dose-limiting pathology in normal somatic tissues. In-depth analysis of the T cell response in patients successfully treated with ex vivo expanded, autologous tumor infiltrating leukocytes (TILs) showed that T cells targeting neoepitopes encoded by the tumor mutanome may be more suitable for combating solid tumors. A clear advantage is that these T cells target truly tumor-specific antigens (TSAs), thereby avoiding the on-target destruction of normal somatic cells or tolerance. The vast majority of the TSAs, however, are patient-individual neoepitopes, requiring highly personalized approaches to identify relevant TSAs and to probe their recognition by TILs. Moreover, prior to re-infusion to patients, unspecific cytokine driven in vitro expansion of TILs, routinely applied in TIL therapy, inevitably leads to a loss of potentially TSA-specific T cell clones, diminishing the efficacy of cellular TIL therapies.
Here, T cell receptor (TCR)-transgenic T cell therapy provides a valuable alternative since a) transgenic T cells target known and defined antigens, b) TSA-specific transgenic T cells can be additionally genetically modified to enhance T cell responses, c) in contrast to TIL therapy, the re-infusion of a monoclonal TCR-transgenic T cell product allows exact enumeration of truly tumor-reactive T cells and d) defined TCR alpha or beta sequences facilitate analysis of T cell fate and dynamics.
Gliomas, tumors with low mutational burden, contain only 30 – 50 non-synonymous mutations. Recently, two multinational and multicenter glioblastoma (WHO grade IV gliomas) vaccine consortia, The Glioma Actively Personalized Vaccine Consortium (GAPVAC) and The NeoVax Consortium, respectively, independently reported successful induction of highly personalized TSA-specific T cell responses in glioblastoma patients. Nevertheless, these studies indicated that highly personalized TSA-specific approaches are a) extremely laborious, b) time-consuming especially in the context of rapid progressive malignancies, and c) restricted to few academic centers.
Here we propose to exploit TCR-transgenic cellular therapies targeting shared T helper cell neoepitopes for brain tumor immunotherapy. With the broad accessibility of next generation sequencing, homogenously expressed genes harboring somatic mutations with high variant allele frequencies in tumors have been identified. Some of these mutations occur in so-called hot spots, show stable expression in primary and relapse situations, and are uniform. From an immunological

perspective, these are ideal targets for therapeutic exploitation; from a genomic and metabolic view, these somatic tumor-specific mutations are considered as oncogenes with an underlying key tumorigenic molecular biology. Uniform, shared, and stable point mutations in the genes of isocitrate dehydrogenase 1 (IDH1) and capicua transcriptional repressor (CIC) frequently occurring in low grade and anaplastic gliomas, have been found by the applicant to result in major histocompatibility complex (MHC) class II-restricted neoepitopes. In preclinical experiments, the applicant has shown that functional TCRs targeting these neoepitopes derived from these clonal driver mutations can be retrieved and exploited in an immunotherapeutic fashion. In the context of two phase 1 clinical peptide vaccine trials, the applicant aims at establishing TCR-transgenic T cell therapy against mutant IDH1 and CIC in a bench-to-bedside-to-bench paradigm applying human avatar mouse models, single cell TCR (scTCR) sequencing, and in silico TCR deep learning tools for secondary sequence optimization. This project will not only apply innovative medium-throughput technologies to establish a new framework of shared tumor-specific TCR warehouses but holds great promise to result in an efficacious therapeutic strategy for immunologically challenging malignancies such as primary brain tumors.