Dieter Kabelitz

Professor Dieter Kabelitz is an eminent immunologist with an impressive career spanning over 50 years. He served as a full Professor at the University of Kiel and was the Director of the Institute of Immunology from 1999 to 2018. Dieter continued his career as a Senior Research group leader at the Institute for Immunology of the University Hospital Schleswig-Holstein Institute of Immunology (UKSH) at the University of Kiel, Germany. He focuses on the functional characterization of γδ T cells. Specifically, he explores strategies to enhance the effector functions of these cells for potential use in cancer immunotherapy. Prof. Kabelitz has been involved in several educational and scientific organizations, including serving as the president of the German Society for Immunology and as a council member of the International Union of Immunological Societies (IUIS). Dieter is currently the past-Chair of the IUIS Education Committee, and he has been involved in building IUIS courses for many years.

What sparked your interest in immunology?

This happened when I worked for my MD thesis in a laboratory of experimental haematology at the Technical University in Munich. We used the – at that time – "innovative" technology of rosette formation between human T cells and sheep erythrocytes to isolate T cells from patients with B-cell malignancies to study their proliferative capacity in response to mitogens, almost 50 years ago….

How did you specifically begin studying γδ T cells?

I got interested in studying gd T cells when we identified CD3-positive T cells in foetal human thymocyte preparations which lacked surface expression of the ab TCR as detected by pan-ab TCR antibody BMA031 (J. Exp. Med. 1988). Subsequently, we generated monoclonal antibodies against various human Vg chains which allowed us to characterize the complete expressed Vg repertoire by flow cytometry. I was fascinated by the capacity of gd T cells to simultaneously recognize (and kill) many different tumour target cells but also infected cells.

What are the key challenges in harnessing γδ T cells for immunotherapy, and how can we overcome them?

The key advantage of gd T cells is their HLA-independent mode of antigen recognition. This makes it possible to apply gd T cells in adoptive cell therapy across HLA barriers. In fact, the use of allogeneic gd T cells expanded from healthy donors for treatment of cancer patients is now in clinical studies. Key challenges of gd T-cell immunotherapy is perhaps the insufficient effector activity of unmodified gd T cells. Multiple strategies are in clinical development to improve the efficacy. These include the design of bispecific T-cell engagers which specifically target gd T cells to selected tumour-associated antigens or the transduction of gd T cells with chimeric antigen receptors (CAR) which again target gd T cells specifically to tumour cells. Other challenges are not

specific for gd T cells but also impact the efficacy of gd T-cell immunotherapy, such as the immunosuppressive tumour microenvironment (TME). Multiple strategies can be envisaged to counteract the TME, including checkpoint inhibitors, innate stimuli like STING ligands to initiate a pro-inflammatory micromilieu and many others.

How do γδ T cells contribute to immune surveillance and protection against infections?

Human gd T cells recognize small pyrophosphates which are produced by many bacteria and some parasites. Interestingly, transformed cells also produce increased amounts of endogenous pyrophosphates which are also sensed by gd T cells. The recognition of homologous "phosphoantigens" derived from microbes and cancer cells explains why gd T cells play a role in anti-infective but also in anti-tumour immunity. We now understand in quite some details how such phosphoantigens activate the gd T cells. Importantly, there is an absolute requirement of transmembrane butyrophilin molecules. Phosphoantigens bind to intracellular regions of butyrophilin BTN3A1 which leads to interactions with BTN2A1 eventually resulting in alterations of the extracellular conformation of BTN3A1/2A1 which then triggers gd T-cell activation. Surprisingly, mouse gd T cells cannot recognize such phosphoantigens. Stress-induced molecules and butyrophilin-like molecules play important roles in governing local immune surveillance by gd T cells in the mouse but also in humans.

What recent breakthroughs or advancements in cancer immunotherapy excite you the most?

Surely, the introduction of bispecific T-cell engagers, checkpoint inhibitors and CAR T cells have revolutionized cancer immunotherapy. However, we are aware that these strategies work best in haematological malignancies and some but other solid tumours. A lot of efforts are devoted to identifying biomarkers which would allow us to predict the

responsiveness of individual patients. Personally, I'm very excited about the perspective of gd T cells in cancer immunotherapy. The use of allogeneic gd T cells will allow to establish cell bank repositories where frozen gd T cells can be made available whenever needed. Such gd T cells can then be used in unmodified form or can be modified by CAR transduction etc.

Could you describe the goals and mission of the IUIS EDU Committee?

The mission of EDUC is to advance immunology training worldwide and specifically to promote and support immunology education in low-to-middle income countries. We do this by organizing one-week in-person courses with a focus on Africa and Latin America, but we have recently also expanded our activities to countries of the FIMSA region like India and Iran. Our courses are very interactive, and the faculty usually stays during the week of the course to facilitate optimal interaction of students with faculty. In-person courses include a mandatory online pre-course which helps to bring the participants to the approximately same level of knowledge. We also provide on-going academic mentoring of previous course participants.

As the past-chair of the IUIS EDU Committee, what initiatives did you champion during your tenure?

The EDU Committee is a team of immunologists from around the globe with a key interest in promoting education in immunology. There is gender equality and representation in all regional federations of IUIS. While the chair is leading the committee, all activities are the joint efforts of a great team. So far, the topics of courses in Africa and Latin America had a focus on infections and tumour immunology, with adjustments to local needs. For last year's course in India, I proposed "Epigenetic regulation of the immune response" as a topic. This is a timely topic which raised great interest. The

Indian experts as members of the Immuno-India faculty are currently preparing an extended online course where some of the widely used bioinformatic tools are taught with practical exercises. This may develop as a role model for future combinations of in-person and online courses.

What challenges did/do you encounter while organizing immunology courses in the Low-and-Middle-Income Countries (LMICs)?

The most important issue is to have a dedicated local team of organizers. In this respect, it’s been a great pleasure to collaborate with all the local teams in recent years. And securing sufficient funds to run a course can be quite a challenge. The funds provided by IUIS, and regional federations are not enough to cover the expenses, so we have always been reaching out to other foundations and companies in search of financial support. Our aim is that participants should not have to pay (except perhaps for a small registration fee). Several years ago, I managed to receive a generous grant from the Volkswagen Foundation which covered all expenses for three courses in West Africa, but this was rather exceptional.

If you could collaborate with any historical immunologist (living or not), who would it be and why?

It would be Charlie Janeway. He introduced the concept of pattern recognition receptors as sentinels of the innate immune system, and various classes of such receptors recognizing pathogen- or danger-associated molecular patterns have been identified as key molecules of innate immunity. Such molecules are also important for initiating and orchestrating subsequent adaptive immune responses. Given that gd T cells are commonly considered to link innate and adaptive immunity (they also express a range of such “innate receptors”), it would be fun to collaborate with Charlie on this topic.

Do you have any advice for young researchers starting out in their career?

Stay curious, be prepared to work hard, read the relevant literature, and – perhaps most important: try to find a really supportive mentor. If you really love doing science: believe in yourself and don’t give up!

Interview by Bonamy (Bon) Holtak