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Tapping the keg of discovery to advance T cell therapy

Starting on 19 September 2022, the very first ImmunOctoberfest conference took place in Raitenhaslach, Germany, bringing together scientists from all over the world to discuss 'bridging innovation and translation in T cell immunotherapy'.

Welcome to ImmunOctoberfest! After a long hiatus from in-person meetings, through countless COVID-19 quarantines, we are now again able to quench our thirst for lively scientific debate on all things T cells — and drink from the keg of science we did! Once again, we gathered from around the world as friends and colleagues to share unpublished data, receive constructive feedback on the development of novel tools used to further our understanding of T cell differentiation, share conceptual advances in our understanding of T cell fate commitment and the developmental path towards functional memory and exhaustion, and also simply to make a human connection outside a two-dimensional 16:9 format.

Highlighting recent advances and challenges in the field of immunology, the symposia began with a full-day seminar that was tailored towards young scientists but also attracted senior investigators. The meeting then transitioned to 10 main sessions featuring 46 regular plus 5 abstract-selected speakers. Here we share highlights from this meeting, and outline open questions that await further exploration.

Immunology update session with Abul Abbas

A reminder of our community's innate dedication and passion for this field took center-stage at the beginning of the conference, as trainees and established investigators gathered to hear immunology from the thought leader Abul Abbas. His five 60-minute sessions served as a primer for broader discussions that were covered during the conference. This introduction highlighted historical advances and open questions, and also provided a much-needed human connection that helped engage young scientists in a vision of the future for our field. Encouraging trainees to remain in a position to pursue academic advances is a challenge that applies to many fields, not just immunology[1]. Although retaining the next generation of scientists will take more than good-natured banter, the simple act of initiating a conversation between new and established investigators is a good starting point for addressing this global challenge.

While taking us through the history of major immunological achievements over the past 30–40 years, Abul provided insights into the development and function of T cells, B cells and the cross-talk between innate and adaptive immunity, and highlighted individuals who have made major contributions to this field. He went on to introduce classical immunological concepts, including immune tolerance and regulation, as well as recent advances in cancer immunotherapy, with particular attention given to the idea that successful immunotherapy requires a full understanding of underlying biological processes.

> **"My experience is that scientists get focused on whatever they are working on and don't pay much attention to the rest of the field, so an occasional reminder is valuable. Also, I want to emphasize the clinical relevance of basic science." Abul Abbas.**

Translational advances

Transitioning from the introductory pre-meeting lectures, the symposia opened with a session that focused on immunotherapy and clinical outcomes chaired by Ben Youngblood. The theme was rigorously explored by Stephen Gottschalk, John Wherry, Dirk Busch, Pablo Umana, Caitlin Zebley and others investigating how T cell therapies can be improved. These researchers dove into one of the dominant themes of the conference, which was tackling the question of how T cell exhaustion (for example, in CAR-T cell therapy or in the tumor context) might be prevented or reversed. This fundamental question and the underlying molecular mechanisms and metabolic signals that contribute to T cell exhaustion, as well as emerging therapeutic strategies, were also touched on by many others from various biological vantages in the following sessions, including a description of the ongoing checkpoint blockade efforts at Genentech and a wonderful discussion from Ping-Chih Ho.

Developmental decisions and fate commitment

An emerging area of research that many attendees focused on was the mechanisms underlying cell fate decisions that affect T cell longevity and terminal differentiation. We heard from Rafi Ahmed, Pablo Umana, Ira Mellman, Axel Kallies and several others about signals that contribute to the self-renewal and advancement of T cells along the developmental path towards terminal T cell exhaustion. In this section, new therapeutic tools exploiting IL-2 signaling were described in the context of modifying the fate commitment of progenitor exhausted T cells[2–4] (and unpublished data). Andrea Schietinger discussed T cell differentiation states and fate determinants in the chronic T cell-driven autoimmune disease type 1 diabetes[5], and Vijay Kuchroo and Christina Zielinsky taught us about regulators of type 17 helper T (T_H17) cell fate[6,7]. Dave Masopust shared an exciting 'multi-lifetime' T cell experimental scheme, in which iterative adoptive transfer and boosting of mouse memory T cells over a decade was used to demonstrate that T cells can expand well-beyond all established replicative bounds. Furthermore, he and Ben Youngblood are leveraging this multi-lifetime model to define T cell senescence-resistance programs (unpublished observations). Spanning the gap between fundamental biology and translational application, we heard from Stephen Gottschalk, Jesus Corria-Osario,

Fig. 1 | The venues. Top: The TUM Science & Study Center Raitenhaslach is located in the former Cistercians monastery founded in 1143. It combines Romanesque and Baroque architecture, and serves to connect the promotion of scientific ideas. The meeting took place in the historical Aula maior, the former ceremonial hall of the monastery of Raitenhaslach. Bottom: After three packed days of intense science, the meeting finished with a concert on the historic organ in the church of the former monastery and a visit at the Oktoberfest, which had opened for the first time after the pandemic.

Dirk Busch and Caitlin Zebley (mostly unpublished data) about how they are using human experimental systems and/or clinical samples to define mechanisms that limit T cell proliferation in response to chronic viral infection and cancer[8].

Immunometabolism and cell differentiation

In the immunometabolism session, Greg Delgoffe, Ping-Chih Ho and others provided insights into T cell intrinsic and tumor microenvironment amino acids and metabolites that promote the development of T cell exhaustion and restrict anti-tumor responses. They covered specific characteristics of the tumor microenvironment that contribute to exhausted mitochondrial phenotypes and impaired anti-tumor $CD8^+$ T cell responses[9,10]. Erika Pearce and Andreas Bergthaler identified metabolic regulators of $CD8^+$ T cell activity and shared unpublished data on the cellular utilization of intracellular metabolites that enhance T cell effector fitness and function. Martin Väth spoke about a glycolytic–epigenetic signaling axis that enables T_H17 cell reprogramming and differentiation[11], and Monika Wolkers and others investigated the use of specific molecular pathways as effectors of human $CD8^+$ T cell differentiation[12]. The $CD4^+$ T cell field was well represented by Shane Crotty, Michael Lohoff, Shohei Hori and many others who identified molecular controllers of $CD4^+$ T cell differentiation.

Tissue homing and residency

Tissue immunity and tissue-specific adaptation of immune responses was covered over two sessions. Percy Knolle, Patrick Bertolino, Matteo Iannacone and others provided insight into the metabolic, molecular and cellular effectors of T cell-mediated immune pathology in the liver. Thomas Korn shared data looking at the function of tissue imprinting of lymphocytes in affecting immunopathology[13,14], and Li-Fan Lu elaborated on the contribution of tissue-resident regulatory T cells to the maintenance of intestinal homeostasis[15]. Dietmar Zehn, Klaas van Gisbergen, Thomas Gebhardt and others presented new tools that can be used to address long-standing questions related to the origin and differentiation of tissue-resident memory T (T_{RM}) cells, with Dietmar Zehn showing a fate-mapping tool that can track the origin of T_{RM} cells and their possible derivatives inside tissues, revealing a limited expansion of $CD103^+$ T_{RM} cells in secondary infections[16,17]. Donna Farber transitioned the discussion to focus on T cell effector and memory differentiation in humans, sharing exciting data on the phenotypes, localization patterns and the heterogeneity of T_{RM} cells among peripheral tissues, with a particular focus on the establishment of the T cell compartment in conjunction with microbial colonization after birth.

We also heard exciting presentations from Jürgen Ruland, Klaus Okkenhaug, Wolfgang Schamel, Paul Thomas, Annette Oxenius, Thomas Höfer, Magdalena Huber, Martin Prlic, Enrico Lugli, Robert Thimme, Douglas Green, Frederica Sallusto, Yamamura Takashi, Sandra Milasta, Luca Gattinoni, Luigia Pace and the travel-stipend awardees Mariana Borsa and Martina Palatella, all of which inspired lively debates during and after the seminar.

Other highlights

Special highlights of the meeting (Fig. 1) include a picturesque location in the old monastery of the Technical University of Munich (TUM) Science & Study Centre Raitenhaslach, the award ceremony for the four winners of the Boehringer Ingelheim travel scholarship, a visit to a Baroque church for a special introduction into its history, followed by an organ concert performed by the former TUM president Wolfgang Herrmann, and a visit to the Oktoberfest in Munich, ending with a private lecture by Vijay Kuchroo on the bus heading back to the venue after a splendid afternoon in a huge Oktoberfest tent.

Face to face again

With this conference, it was our intention to bring back the spirit of in-person collegial scientific exchange, where unpublished data are presented and discussed intensely; where direct interaction between speakers and the audience is possible; and where speakers and members of the audience can engage in extended conversation during session breaks and evening social events. These fundamental features of in-person conferences might be taken for granted by many of us, but many younger attendees might not be so acquainted with these experiences owing to the halt on conferences that occurred during the COVID-19 pandemic. Science is more than reading papers, listening to Zoom talks and sitting in the same desk and office every day. We hope this meeting and others like it can revitalize this spirit of collaborative science. Indeed, we plan to continue this meeting series at the same location in Raitenhaslach/Burghausen,

Germany, with our next meeting planned for 22–27 September 2024.

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Competing interests

The authors declare no competing interests.