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*Published in:*
Transplantation

*DOI:*
10.1097/TP.0000000000003132



*Publication date:*
2020

**Transplantation Publish Ahead of Print**

**DOI: 10.1097/TP.0000000000003132**

# The First International Transplant Science (ITS) Meeting

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**Abstract**

The first International Transplant Science (ITS) meeting jointly organized by AST, ESOT and TTS was held on November 10-13, 2019 in Clearwater, Florida, to focus on issues related to the basic and translational science of immunology and transplantation. The 148 participants included international experts in transplantation, immunology, cell biology and organ engineering, as well as young investigators and trainees in these areas. The objectives of the meeting were to (1) introduce and discuss the latest discoveries, technologies and concepts in basic science of relevance to transplantation; (2) provide opportunities for every trainee and young investigators to present their work in mini-oral and mentored poster sessions; (3) have programmed networking opportunities to allow for the free exchange of ideas and developing new collaborations. Participants came away from the meeting inspired by the quality of science presented, excited by the opportunities to discuss science with fellow attendees, and enthusiasm for the next ITS meeting in 2020 in Europe.

Over the past 3 decades, basic transplantation science symposia were designed to be small meetings held in a remote location, that emphasized high-quality basic science and featured opportunities for informal interactions between the invited experts, established researchers, young investigators and trainees. These meetings were first organized as biannual meetings by The Transplantation Society (TTS) since 1987, and in collaboration with the European Society for Organ Transplantation (ESOT) from 2009-13. The American Society of Transplantation (AST) recognized the need for meetings focused on the basic transplantation community, and jointly organized the BeST16 meeting in 2016 with ESOT. Following these meetings, the chairs of the basic science committees of AST, ESOT, and TTS agreed on the need to cohost a single basic and translational International Transplantation Science (ITS) meeting on an annual basis and with alternating locations between North America and Europe for a 3-year trial period. This concept received strong support by the Boards of each of the 3 societies, with the vision of global collaboration between scientists working to improve transplantation outcomes.

The first ITS meeting started with a premeeting workshop "Advancing Transplantation Science with Single Cell Analysis", that aimed at critically assessing the technologies, currently available or under development, that can be used to understand the phenotype and function of leukocytes at the single-cell level to enrich transplantation studies. State-of-the art B cell receptor (BCR) sequencing (Nina-Luning Prak, University of Pennsylvania) showed that B cell clones distribute into 2 broad networks in the gastrointestinal tract or in the blood, bone marrow, spleen and lung.[1] High-throughput T cell receptor (TCR) sequencing (Megan Sykes, Columbia University) was used to identify the fate of donor-specific T conventional and regulatory T cells (Treg) in kidney[2] and liver transplant recipients.[3] Understanding how to use the various single cell next-generation sequencing (NGS) technologies and analyzing the data remains challenging. Eliver Ghosn

(Emory University) discussed the merits, drawbacks and pitfalls of standard RNA sequencing technologies, CITE-Seq (Cellular Indexing of Transcriptomes and Epitopes by Sequencing) and SuPERRseq (Surface Protein Expression, mRNA, and Repertoire sequencing), and usefully covered the pipeline for data analysis using the Seurat R package.[4] Niroshan Ramachandran from nanoString Technologies introduced the new GeoMx Digital Spatial Profiling (DSP) technology, which is capable of multiparameter RNA or protein-protein analysis of cells with spatial and morphological context directly on formalin-fixed paraffin-embedded tissue samples. This technology has demonstrated a great value in cancer studies[5]; the application to transplant biopsies is likely to yield new insights into mechanisms of clinical rejection. Finally, our ability to visualize up to 100 markers in cells by flow or mass cytometry has resulted in a need to analyze and present the huge amount of acquired data. Lisa Borghesi (University of Pittsburgh) introduced an array of analytical methods including tSNE (Stochastic Neighbor Embedding)[6] for single cell resolution, SPADE (Spanning-tree Progression Analysis of Density-normalized Events)[7] or FlowSOM (Flow or mass cytometry data using a Self-Organizing Map)[8] for trees of relationships, and Citrus (cluster identification, characterization, and regression)[9] for clustering followed by linear regression. This workshop underscored the need for basic and translational researchers to keep up with the rapidly evolving newest technologies.

The main scientific sessions focused on cutting-edge research innate and adaptive immunity, organ engineering and transplantation therapeutics. Talks in the Innate Immunity session revealed the complex roles innate cells play in nontransplant and transplant settings. Dmitry Gabrilovich (Wistar Institute) provided a broad overview of the importance of the different types of myeloid-derived suppressor cells in the regulation of immune responses in cancer. Dan Kreisel (Washington University of St. Louis) discussed the flood of neutrophils into the lung that

contributed to leaky endothelial cell barrier and ischemia reperfusion injury. Joseph Sun (Memorial Sloan Kettering) discussed avidity selection and the molecular and epigenetic mechanisms that mediate NK cell memory in the context of herpes infection. Finally, Xian Li discussed novel findings of the involvement of the paired Ig-like receptor A (PIRA) and PIRB as stimulatory and inhibitory receptors respectively, and that recognize MHC Class Ia. Importantly, PIRA blockade prevented chronic rejection and PIRA is polymorphic, suggesting it may play a role in transplant outcome. Taken together, this session highlighted the many open areas of investigation into how innate cells affect transplantation rejection.

The importance of adaptive immunity to transplantation was underscored in 3 sessions. Recent reports that stable graft acceptance after weaning of immunosuppression can be achieved in rare kidney transplant recipients and more frequently in liver transplant recipients, as well as following combined stem cell and kidney allograft transplantation, have provided hope that transplant tolerance is achievable in the clinic and have been an impetus for investigations into novel mechanisms of T cell tolerance and dysfunction. Caitlin Zebley (St. Jude Children's Research Hospital) discussed how DNA methylation is mediating the epigenetic modifications required for imprinting T cell exhaustion. Mary Phillip (Vanderbilt University) discussed how the nuclear factor TOX induces the expression of T cell dysfunctional genes in tumor-specific $CD8^+$ T cells, including PD-1 and TCF-1, but not the loss of effector function (IFN□ production). Her findings highlight a dissociation between the phenotype of T cell exhaustion and actual loss of function, and the need to understand how loss of effector function is enforced. The role of PD-1 in diabetogenic $CD4^+$ T cells in restraining T and B cell responses was discussed by Brian Fife (University of Minnesota), while Maria-Luisa Alegre (University of Chicago) discussed new findings on how alloreactive $CD4^+$ T cells regulate expression of the

chromatin organizer SATB1 to promote transplant rejection versus tolerance. Collectively, talks in this session pointed to a common theme of epigenetic reprogramming of $CD4^+$ and $CD8^+$ T cells away from memory and into exhausted and/or dysfunctional cells, that may lead to new approaches for preventing rejection and inducing transplantation tolerance.

Successful treatment of T cell-mediated rejection may result in increased tissue-resident memory T cells that poise the graft for subsequent acute or chronic rejection. In this context, Jacob Kohlmeier (Emory University) described lung tissue-resident memory T cells that can be distinguished phenotypically and transcriptionally as airway- versus interstitium-resident T cells. Airway T cells were prone to apoptosis perhaps because of greater nutrient starvation, providing a reminder of how the local environment affects local immune function. Qhizi Tang (University of California at San Francisco) discussed islet graft-infiltrating Treg and their distinct antigen specificity from that of infiltrating conventional T cells, and the protection to islet allografts provided by the delayed therapeutic transfer of Treg. Heth Turnquist (University of Pittsburgh) presented the role of the local production of IL-33 by lung epithelial cells in stimulating graft-infiltrating Treg to secrete IL-13, which in turn limited acute inflammation and lung injury. Finally, Marcus Clark (University of Chicago) focused on human renal transplant-infiltrating B cells captured and analyzed at the single cell level, provided evidence of the accumulation of autoreactive B cells and raising the possibility that the local inflammation in the allograft might facilitate a break in B cell tolerance. Overall, this session stressed that discrete functional differences of infiltrating cell subsets may be shaped by their antigen specificity and the local tissue environment.

The influence of the microbiota on transplant immunity is becoming increasingly appreciated, as well as the effect of antibiotic use. Elizabeth Mann (University of Manchester) discussed how antibiotics can increase the responsiveness of macrophages and their ability to promote Th1 responses in the colon, resulting in inflammatory responses that are ineffective for bacterial infections that depend on Th17 and Th2 immunity. Notably, this effect is reversed by treatment with the short chain fatty acid butyrate. Along similar lines, Jay Kolls from Tulane University discussed the ability of vancomycin-mediated disruption of the gut microbiota to reduce the pulmonary Th17 response necessary to clear fungal infections, demonstrating systemic effects of the intestinal microbiota. Finally, Jerzy Kupiec-Weglinski (UCLA) reviewed the ability of antibiotics to reduce the severity of ischemia/reperfusion injury after liver transplantation in mice, and the correlation between antibiotic treatment and diminished early liver allograft dysfunction in the clinic. The postulated mechanism was dependent on endoplasmic reticulum stress and autophagy pathways. This session highlighted the influence/mechanisms of intestinal microbial composition and antibiotic use on local and distal immunity and transplant outcomes.

The Sex in Transplantation session focused on a clinically important and often overlooked variable, namely the effect of sex. Alexander Chervonsky (University of Chicago) discussed how sex differences, through sex hormones, affect the microbiota, which in turn affects T cells and the development of autoimmune diabetes in NOD mice. Montserrat Anguera (University of Pennsylvania) showed how the inactivation of the X-chromosome is necessary in cells with 2 X chromosomes, and that this is mediated by the X inactive specific transcript (XIST). XIST RNA disappears in mature resting T and B cells but reappears upon activation. Immunologically important genes such as FoxP3, CD154, TLR7/8 and IRAK1 are located on the X chromosome, leading to the speculation of "plasticity" of T and B cells in females while supporting the concept

that XIST -independent inactivation of 1 of the pair of X chromosomes may provide a more robust immunity and increased susceptibility to autoimmune disease in females. Finally, Paige Porrett (University of Pennsylvania) discussed the effect of pregnancy in inducing $CD8^+$ T cell exhaustion, and how these findings may have implications to multiparous transplant recipients. Overall this session underscored the importance in considering sex in transplantation, and provided mechanistic insights into how sex shapes the immune responses to allogeneic transplantation by intrinsically altering the immune cells, or indirectly through hormones, microbiota composition and pregnancy.

The importance of B cells and antibodies was highlighted by Robert Fairchild (Cleveland Clinic) who discussed data underscoring the importance of NK cells in an experimental model of acute antibody-mediated rejection. Intriguingly, the presence of donor-specific antibody resulted in chronic antibody-mediated rejection in animals lacking NK cells, thus providing a new experimental model for investigating a critical problem in clinical transplantation. Eric Meffre (Yale University) provided an overview of B cell tolerance and discussed the potential of autoimmune diseases interfering with those effects. In general, autoimmune diseases can be categorized into those with defects in central B cell tolerance, resulting in the escape of autoreactive immature B cells, and defects in peripheral B cell tolerance which is usually due to defective T cell tolerance and regulatory T cells. These observations have direct implications to the induction of transplantation tolerance, and suggest that the culling of immature alloreactive B cells is critically dependent on their encountering alloantigen in the bone marrow. Finally, Frances Eun-Hyung Lee (Emory University) provided an overview of the long-lived plasma cells that survive in specialized niches in the bone marrow comprising mesenchymal stem cells, the cytokine APRIL, and a hypoxic microenvironment. Novel approaches for maintaining long-

lived plasma cells in vitro provide opportunities for their quantification, and for identifying new targets for depleting the cells responsible for long-term humoral sensitization.

There is clearly a need for organ conditioning either pretransplantation or posttransplantation after immune and ischemic injury has eroded the quality of the transplantation organ. This important area of transplantation research was presented by Paulo Martins (University of Massachusetts) discussing the approach of RNA interference during machine perfusion of liver allografts under both hypothermic and normothermic conditions, to limit ischemia reperfusion injury. Jason Wertheim (Northwestern University) discussed the use of extracellular matrix scaffolds for renal tissue development that might have efficacy. Alex Soto-Gutierrez (Pittsburgh University) talked about the benefits of reintroducing the gene HNF4□ in hepatocytes from rat end-stage liver disease to restore expression of liver function genes in vitro and to normalize liver function in vivo, supporting the interesting concept of the reversibility of fibrosis and the enticing possibility of repairing organs rather than transplanting new ones.

Keynote speakers are selected to inspire and challenge the audience to think more deeply and out of the box. Both Keynote speakers did just that in different ways. Katherine High (Spark Therapeutics) inspired by describing her successes in moving gene therapy to patients, underscoring a theme of the ITS meeting of how outstanding science evolves into clinical therapies. Douglas Green (St Jude Children's Research Hospital) closed out the meeting with a fantastic talk on the 3 major ways a cell dies: murder (freeze-thaw, complement-mediated lysis, cell-induced cell death), suicide (apoptosis, necroptosis, pyroptosis) or sabotage (ferroptosis, parthanatosis, lysosomal cell death). He reminded us that how a cell dies affects immunity; for example, apoptotic cells picked up by dendritic cells can mature into antigen-presenting cells capable of cross-priming $CD8^+$ T cells but not $CD4^+$ T cells. He inspired us to challenge long-

held paradigms, and tasked us to test whether controlling the way a cell dies might lead to better prevention of rejection and the induction of transplantation tolerance.

The small meeting format with outstanding scientific presentations once again proved its value by keeping the entire audience together, engaged and interactive. It provided a unique opportunity for trainees to present their findings to the transplant community and receive feedback; every accepted abstract was discussed in a 2 minute and 3 slides elevator pitch. In the end, attendees were exposed to novel concepts that could be adopted into their own research thinking, and new approaches that could be used to delve into the mechanisms that control immune cell function, both systemically and within transplanted organs. Attendees came away challenged, inspired, motivated and eagerly looking forward to the next ITS meeting planned to be held in Europe in November 2020.

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