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The 2020 FASEB Science Research Conference on Translational Neuroimmunology: From Mechanisms to Therapeutics, June 29-30, 2020

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The nonprofit Federation of American Societies for Experimental Biology (FASEB) sponsors a series of Science Research Conferences (SRCs) each year. These conferences offer scientists a collegial and relaxing environment to discuss and explore new findings and approaches to specific research areas.

The Translational Neuroimmunology Conference: From Mechanisms to Therapeutics was held June 29-30. This meeting was FASEB's first SRC that was conducted via a fully virtual format, consequent to the COVID- 19 pandemic. It was originally scheduled to be held on July 19-22 at the Babson Executive Conference (Babson, MA. USA), before FASEB leadership made the difficult decision to cancel all in- person SRCs through the summer and strongly encouraged organizers to conduct virtual conferences. When we were asked to organize the first virtual conference, we were initially concerned about changes to scientific content, mode of presentation, and opportunities for interactions between the session chairs, speakers and audience. Nevertheless, we decided to proceed, in light of the importance of

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Dr. Cohen led off the meeting with an outstanding state-of-the-art overview of disease-modifying therapies (DMTs) for the human demyelinating disease MS. He addressed several issues related to unmet needs for patients with MS. One question concerned whether it is more beneficial to treat newly diagnosed patients with highly potent DMTs that carry higher risks, as opposed to initiating less potent but safer drugs and escalating as needed. Available DMTs for patients with the relapsing-remitting form of MS are not as effective in progressive MS, and do not promote repair of the damaged CNS nor functional recovery. Dr. Cohen's talk concluded by indicating that continuing efforts are needed to develop better methods for evaluating both disease activity and treatment responses in patients with both relapsing and progressive forms of disease.

Dr. Pratt discussed a pilot study in which peripheral blood mononuclear cells from patients with MS and healthy control subjects were subjected to in depth analysis via 21-color flow cytometry and single-cell RNA sequencing (scRNAseq). This study revealed a relative enrichment of effector memory CD8 T cells in the MS cohort, and an enrichment of CD16⁺CD56⁺ NK cells in the healthy cohort. Second, he discussed scRNAseq studies in MOG-induced murine experimental autoimmune encephalomyelitis (EAE), focused on CNS vascular endothelial cells. Venules were overrepresented, while capillaries were underrepresented, in specimens from mice with EAE versus control mice. The venules in mice with EAE were distinguished by enrichment of genes involved in the cellular response to growth factors and cytokines, and in integrin binding. These findings reveal new pathways that may be involved in leukocyte trafficking and accumulation within the CNS.

Finally, Dr. Engelhardt's talk focused on fluid exchange between interstitial fluid and cerebrospinal fluid in the brain, referred to as the "glymphatic system." She proposed the intriguing concept that the endothelial blood-brain barrier (BBB), the epithelial blood-cerebrospinal fluid barrier (BCSFB), the blood-arachnoid barrier (BAB) and the glia limitans delineate separate compartments in the CNS that differ strikingly with regard to their accessibility by immune cells and their functional connections to the peripheral immune system. Dr. Engelhardt provided fascinating insight into mechanisms by which the BBB directs circulating T cells to unique junctional sites mediated, in part, by signaling through atypical chemokine receptor 1 (ACKR1) on endothelial cells.

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this SRC to the scientific community in neuroimmunology, and to young and emerging investigators in particular. Among the dramatic changes to the meeting format, we reduced the original 9 sessions, spanning a 5-day period, into 4 sessions, spanning 1.5 days. The most difficult task was ensuring that the remaining 4 sessions covered a representative range of cutting-edge topics in discovery-based research and clinical neuroimmunology. When we conveyed the news of the revised meeting format, we were met with overwhelming support and understanding from the invited speakers and chairs, a true testament to the communal and civil ethos of our colleagues. This, in combination with outstanding help from FASEB staff, made the change from an in-person meeting to a virtual format not only possible, but surprisingly smooth.

The revised meeting agenda consisted of 3 keynote talks, 21 invited oral presentations within 4 sessions, and 37 poster presentations. Overall, 50% of the speakers were women, 12.5% of speakers were underrepresented minorities (URMs) and 50% of session chairs were women.

Attendance to the meeting was impressive, exceeding that of former in-person meetings, with 181 registered participants, 57% of whom identified as females, and 11% of whom identified as URMs. In addition, 54% of attendees were Early Career Scientists (defined as faculty with <10 years of experience, postdoctoral associates, and graduate students).

Neuroimmunology is arguably one of the fastest growing fields in biomedical science, from a basic as well as a translational stance. Interactions between the innate immune system and central nervous system (CNS) resident cells play critical roles in neurodevelopment as well as neurodegeneration. While CNS-infiltrating immune cells directly impact the nervous system in the setting of a number of diseases, such as infectious meningoencephalitis, multiple sclerosis (MS), and antiglioma immunity, more is being learned about how the autonomic nervous system modulates peripheral immune responses. An increasing number of neurological conditions, including paraneoplastic syndromes, neuromyelitis optica, and some forms of encephalitis, have been found to be mediated by autoantibodies. The last 20 years have witnessed unprecedented advancements in the pharmaceutical management of neurological conditions with immunotherapies. Hence, there are now over 15 FDA-approved drugs that decrease relapse rates in MS, all of which modulate or target the adaptive immune response. Collectively, the basic discoveries and clinical advancements listed above underscore the widespread interest that Neuroimmunology holds for scientists, physicians, and research and clinical trainees across a range of disciplines, as well as for the general public.

KEYNOTE TALKS

The three Keynote Speakers were Jeffrey Cohen (Cleveland Clinic, Cleveland, OH, USA), Alex Pratt (University of Montreal, Montreal, QC, Canada), and Britta Engelhardt (University of Bern, Bern, Switzerland).

SESSION 1

Session 1 focused on CNS regulation of peripheral inflammation. Valentin Pavlov (Feinstein Institute for Medical Research, Manhasset, NY, USA) discussed the vagus nerve-based

inflammatory reflex, and the role it plays in regulation of immune responses in the context of inflammatory and metabolic diseases. Dr. Pavlov described the anti-inflammatory and disease-alleviating effects of electrical vagus nerve stimulation, and cholinergic pharmacological modalities, including centrally acting acetylcholinesterase inhibitors, such as galantamine.

Dr. Dana McTigue (Ohio State Wexner Medical Center, Columbus, OH, USA) gave a presentation focused on the relationship between spinal cord injury (SCI), chronic hepatic inflammation, and metabolic disruption. Dr. McTigue hypothesized that SCI disrupts regulation of the acute phase response (APR) and prolongs hepatic inflammation. Using a rat spinal contusion model, her laboratory showed that SCI causes rapid Kupffer cell (KC) activation and upregulation of pro-inflammatory cytokines persistent for months postinjury. Liver inflammation after SCI may be an important clinical target to improve the health, and potentially function, of individuals suffering a SCI.

Dr. Partha Dutta (University of Pittsburgh School of Medicine, Pittsburgh, PA, USA) concluded the session by discussing the regulation and differentiation of myeloid progenitor cells by the sympathetic nervous system. Dr. Dutta presented evidence that the frequency of inflammatory myeloid cells correlates with plasma norepinephrine levels in diabetic patients, suggesting the role of sympathetic activation in myeloid cell production. Diabetic mice had increased numbers and proliferation of splenic granulocyte macrophage progenitors (GMPs), the immediate precursors of myeloid cells. He concluded that catecholamines produced by leukocytes in response to sympathetic activation plays an unexpected role in GMP proliferation and myeloid cell generation.

SESSION 2

Session 2 focused on how cells of the immune system can mediate CNS repair. Dr. Veronique Miron (University of Edinburgh, Edinburgh, UK) launched the session with work from her laboratory demonstrating a critical role of microglia in driving remyelination following experimental demyelination. Her laboratory found that remyelination requires a transition of microglia and infiltrating monocytes from a proinflammatory to a proregenerative state, and that ageing impairs this process. The transition apparently occurs via microglia/ monocyte turnover. Proinflammatory microglia and monocytes die by necroptosis and are replaced by new cells with a proregenerative profile via a type-1 interferon-dependent pathway. This study highlights the importance of myeloid cells as therapeutic targets to ensure myelin health in disease and ageing.

Next, Dr. Craig Walsh (University of California, Irvine, CA, USA) presented compelling data that human neural stem cells (hNSCs) engrafted into the spinal cords of mice with established demyelination promote the expansion of neural antigen-specific regulatory T cells (Tregs) that subsequently activate endogenous repair pathways to promote remyelination in a preclinical mouse model of MS. hNSC-expanded Tregs (hNSC-Tregs) are derived from the “exTreg” pool. Intriguingly, hNSC-Tregs display a unique gene expression signature, characterized by high levels of transglutaminase 2, known to facilitate

oligodendrocyte maturation. Hence, Tregs not only contribute to disease remission by suppressing neuroinflammation, but also by promoting CNS tissue repair.

Dr. Andrew Sas (The Ohio State University, Columbus, OH, USA) reported the discovery of a unique immature myeloid cell with neuroregenerative and neuroprotective properties. This cell, which has a distinctive cell surface phenotype and transcriptomic profile, directly rescues injured neurons from death and stimulates the regrowth of severed axons, both *in vitro* and *in vivo*. Dr. Sas and the team at OSU found this cell to induce neuronal survival and axon regeneration *in vivo* in models of optic nerve crush and SCI. This research may lead to exciting advances in novel cell-based therapies that restore neurological function over a range of neurological disorders including traumatic brain and spinal cord injury, ALS, stroke, and MS.

Dr. Byron Ford (University of California, Riverside, CA, USA) concluded the session by arguing that neuregulin-1 (NRG-1) may offer a new treatment for stroke. Dr. Ford demonstrated that NRG-1 reduced ischemia-induced neuronal death and neuroinflammation in rodent stroke models with a therapeutic window of >13 hours. Moreover, NRG-1 administration also resulted in improvement of neurological function when administered 3 days following ischemia, suggesting a role in neuronal repair. Finally, NRG-1 prevented neuronal injury and improved BBB integrity in animal models of brain hemorrhage. These findings clearly aid in the progression of NRG-1 toward clinical trial, FDA approval, and development of a new treatment for ischemic stroke.

SESSION 3

Session 3 was focused on the role of the adaptive immune system in primary neurological diseases. Dr. Eric Lancaster (University of Pennsylvania, Philadelphia, PA, USA) gave a talk centered upon autoimmune encephalitis. This was an outstanding clinical lecture that about the autoantibodies that have been identified in patients with different forms of autoimmune encephalitis within the past dozen years. The targeted autoantigens include CNS membrane proteins, including ionotropic receptors, metabotropic receptors, and cell adhesion molecules. Each autoantibody-mediated disorder has characteristic symptoms that reflect the functions of the target antigens. The autoantibodies cause loss of function of the target receptors, although the precise mechanisms may differ. Clinical disorders associated with misguided antibody attacks on CNS proteins can now be accurately diagnosed through antibody testing, and these diseases also may respond favorably to immune suppression.

The lecture by Dr. Manu Rangachari (University of Laval, Quebec, QC, Canada) examined gender differences and their impact on immune responses in the context of progressive CNS autoimmunity. It has long been recognized that sex differences influence the incidence and severity of MS. However, the underlying cellular and molecular mechanisms for why male sex is associated with more aggressive and debilitating disease remain poorly defined. Dr. Rangachari elegantly demonstrated that sex chromosomal complement, not hormones, is responsible for the increased pathogenicity of male Th17 cells. An X-linked immune regulator, *Jarid1c*, was downregulated in pathogenic male murine Th17 cells. These findings

argue that male sex critically regulates Th17 cell plasticity and pathogenicity via sex chromosomal complement.

The final talk of the session, by Dr. Maria Castro (University of Michigan, Ann Arbor, MI, USA), examined how epigenetic reprogramming in myeloid cells leads to an immune permissive environment in gliomas. Mutant isocitrate dehydrogenase 1 (mIDH1) is present in some patients with low-grade glioma (LGG) and correlated with better prognosis and survival. Dr. Castro showed that mice with mIDH1-positive gliomas have decreased numbers of CD11b⁺ Gr1⁺ myeloid-derived suppressor cells in the TME, bone marrow (BM), blood, and spleen. These studies revealed that mIDH1, through the production of 2HG, modifies the cytokine repertoire in the glioma microenvironment, altering the phenotype and function of the tumor infiltrating specific myeloid cell compartment and rendering them nonimmunosuppressive. This transition occurs in response to activation of the granulocytic differentiation program in the BM by tumor-derived granulocyte-colony stimulating factor (G-CSF). Blocking G-CSF restored the inhibitory function of the granulocytic myeloid cells in mIDH1 and shortened the median survival of mIDH1 mice. Dr. Castro's work provides insights into novel epigenetic alterations triggered by mIDH1, which regulate myeloid cells' heterogeneity and immunosuppression, that can be employed to develop novel immunotherapeutic strategies.

SESSION 4

The focus of Session 4 was to examine the role of innate immune in CNS pathology. Dr. Tim Vartanian (Cornell University, Ithaca, NY, USA) proposed *Clostridium perfringens* epsilon toxin as an environment agent that functions in MS to cause focal opening of the CNS endothelial barrier and early injury to oligodendrocytes/myelin. Indeed, Dr. Vartanian's work revealed that 29% of people with MS versus 2.9% of healthy controls harbor epsilon toxin-producing strains of *C. perfringens* in their gut microbiome. These studies indicate that epsilon toxin induces robust transcytosis in CNS endothelial cells, resulting in focal permeability that induces selective death of oligodendrocytes and demyelination. In summary, Dr. Vartanian's presentation demonstrated a statistical association of epsilon toxin-producing *C. perfringens* strains with MS and provided mechanistic plausibility for epsilon toxin as an environmental trigger for MS.

Dr. Tammy Kielian (University of Nebraska Medical Center, Omaha, NE, USA) spoke next on her laboratory's work studying immunological aspects associated with *Staphylococcus aureus* biofilm that can occur following craniotomy. Dr. Kielian's laboratory has developed a mouse model of *S. aureus* craniotomy-associated biofilm infection that is typified by a unique immune compartmentalization, namely preferential neutrophil recruitment in the subcutaneous galea, whereas monocytes are more prominent in the brain parenchyma. Myeloid-derived suppressor cells (MDSCs), an immature myeloid population with anti-inflammatory properties, are present in both compartments, but are most abundant in the galea. Using sophisticated approaches including 2-photon microscopy, Dr. Kielian demonstrated a complex response to biofilm infection, namely, an initial antibacterial response to control *S. aureus* outgrowth; however, this transitions to a maladaptive immune response that accounts for infection persistence.

Dr. Etty (Tika) Benveniste (University of Alabama at Birmingham, Birmingham, AL, USA) gave an insightful lecture characterizing neutrophil subsets present within the brain during EAE. Both adaptive and innate immunity are regulated by the Janus kinase (JAK)/signal transducers and activators of transcription (STAT)/suppressors of cytokine signaling (SOCS) pathway. The SOCS3 protein inhibits activation of STAT3, STAT1, and STAT4 in a cell-specific manner, thereby terminating signaling through these pathways. Dr. Benveniste's laboratory generated mice that lacked *Socs3* in macrophages and neutrophils, and these animals were subjected to MOG35–55-induced EAE. The animals displayed a nonresolving brain-targeted form of EAE characterized by ataxia and tremors, which correlated with activation of STATs and infiltration of CD4⁺ Th1 and Th17 cells, macrophages, and neutrophils. The researchers next employed scRNAseq to identify distinct neutrophil clusters in the cerebellum with unique transcriptional signatures, and they hypothesized that disease-specific transcriptomic changes occur in neutrophils that lead to pathogenic effector functions specific to brain-targeted EAE.

The final lecture of the session, as well as of the meeting, was given by Dr. Mathew Blurton-Jones (University of California, Irvine) whose laboratory has developed a unique chimeric mouse in which human microglia are present within the CNS. In brief, transplantation of induced pluripotent stem cell (iPSC)-derived hematopoietic progenitors into the brain of hCSF1-immunodeficient mice results in context-dependent differentiation into microglia, acquisition of an ex vivo human microglial gene signature, and responsiveness to both acute and chronic insults. Notably, transplanted microglia also exhibit robust transcriptional responses to amyloid β (A β) plaques that only partially overlap with those of murine microglia, revealing new, human-specific A β -responsive genes. Using CRISPR-mediated targeting of TREM2 in iPSCs, Dr. Blurton-Jones reported that homozygous deletion of TREM2 resulted in impaired microglial migration toward amyloid plaques and this potentially due to impaired CXCR4 signaling. The diminished association with plaques is accompanied by a significant reduction in the number of disease-associated microglia (DAMs) detected by both single-cell sequencing and confocal microscopy. These findings argue that TREM2 plays a critical role in the sensing and migration of human microglia toward amyloid plaques.

PARTICIPANT RESPONSE

Results from the evaluation forms indicated that 95% would attend another FASEB Translational Neuroimmunology SRC. In addition, >97% indicated they would recommend this conference to others. Importantly, > 97% of responders indicated that the virtual platform employed was easy to use, and this is a testament to the hard work and diligence that FASEB employed to ensure the meetings went smoothly.

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Abbreviations

BBB	blood-brain barrier
BM	bone marrow
CNS	central nervous system
DMT	disease-modifying therapy
EAE	experimental autoimmune encephalomyelitis
iPSC	induced pluripotent stem cell
mIDH1	mutant isocitrate dehydrogenase 1
MS	multiple sclerosis
NRG-1	neuregulin-1
SCI	spinal cord injury
scRNAseq	single-cell RNA sequencing
SOCS	suppressors of cytokine signaling
SRC	Science Research Conference
STAT	signal transducers and activators of transcription
Treg	regulatory T cell
URM	underrepresented minority