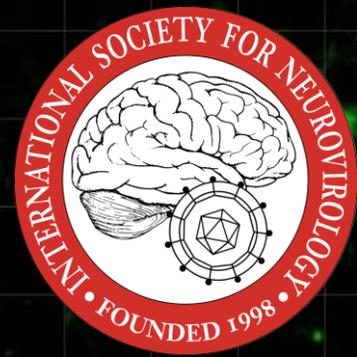


NEWS IN NEUROVIROLOGY

Official newsletter of the
International Society for NeuroVirology

Editor: Tory Johnson, PhD | Associate Editor: Fred Krebs, PhD



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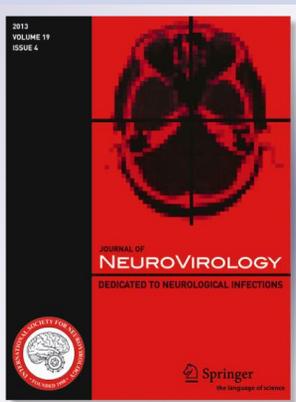
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**Journal of
NeuroVirology**

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A message from the President

By Bruce Brew

The 17th International Symposium on NeuroVirology and the 2021 Conference on HIV in the Nervous System was held virtually this past June. As with other important scientific gatherings, an in-person event was not feasible due to COVID-19. Using a combination of the platform Gather.town and Zoom, a three day virtual symposium occurred that showcased cutting edge topics such as COVID and the Brain (covering both clinical and basic science overviews), Emerging Pathogens, HIV (Cure and Aging/Co-Morbidities) and timely topics in Neurovirology.

This first virtual gathering was a tremendous success, with close to 200 registered attendees. The symposium consisted of 102 poster presentations, five scientific sessions, eight plenary speakers, and one special event. A total of 27 speakers took to the platform to present their work. To cap off the opening day, Dr. LaMisha Hill, Director of Multicultural Affairs, Office of Diversity and Outreach, University of California, San Francisco, led a discussion addressing the topic of “Unconscious bias”. This was a relevant subject among our attendees and a lively conversation ensued.

Additional highlights included an interactive poster session where the presenters engaged with attendees in real time. Colorful Avatars could be seen scurrying about the virtual space which included four separate rooms for presentations, several lounges and my favorite location, a beach where the sound of receding waves could be heard from the “Pacific” (appropriate given where I live!). As always, an important aspect of the meeting was the emphasis on trainees. This year, eight dynamic junior investigators presented their latest research and covered critical topics such as animal models, lentivirus, HIV and AD, and gut-brain in NeuroHIV, among other important areas of study.

I am most grateful to all those who attended the symposium and presented their novel research via this unique virtual atmosphere.

It is my hope that we return to our usual in-person gathering for the Fall 2022.

Lastly, on a sad note, we lost a dedicated ISNV member, Dr. Randy Cohrs, in July. Dr. Cohrs was a regular meeting attendee, and a consistent member since ISNV’s inception in 1998. Randy was not only an excellent scientist, but also had great talent as a meeting

(Continued on page 2)

Message from the President

Continued from page 1

planner, organizing his Colorado Alphaherpesvirus Latency Symposium (CALs) every year in Vail, Colorado. Randy learned quickly about the virtual meeting world and thought nothing of sharing his knowledge. He brought our team up to speed on this new age and worked tirelessly with our planners in organizing our virtual ISNV gathering with countless Zoom meetings and dry runs on the Gather.town site. We remember him as a valued colleague and dear friend.



Dr. Randall Jay Cohrs
February 11, 1952 – July 30, 2021

ISNV highlights research in COVID and Emerging Infections

By Avindra Nath, M.D.

*Section of Infections of the Nervous System, National Institute of Neurological Disorders and Stroke
National Institutes of Health, Bethesda, MD*

The ISNV meeting this year was held virtually and one full day was devoted to emerging infections. The first session was devoted to COVID and the brain. This includes five talks that covered the clinical manifestations, the neuropathology, animal models and neuropathogenesis. Considering the virus was first discovered only over a year ago, it is remarkable how much progress has been made over such a short period of time. Yet the speakers also highlighted many unanswered questions. For example, while the virus has the ability to infect brain cells in vitro and in transgenic animal models, it remains perplexing why the virus itself can only rarely, if at all, be detected in the brain. The mediators of the profound neuroimmune response and damage to the neurovascular unit remain poorly understood. The long-term complications of the virus have been termed Long-Haul COVID which manifests as a complex compilation of symptoms including brain fog, dysautonomia, pain syndrome and exercise intolerance. Realizing the severe socio-economic consequences of this syndrome, the US Congress has approved over one billion dollars for research on this syndrome. Members of the ISNV are well positioned to apply their expertise in viral pathogenesis to take advantage of this funding opportunity and make a real difference in the understanding of this illness.

The second session of the meeting was devoted to other emerging infections. The ISNV realizes that COVID-19 is not the last pandemic that we will face, but rather pandemics are a continuum. We need to understand the plurality of viruses that have the potential of causing pandemics. Most of these are neurotropic viruses. Hence it was fitting that talks in this session were devoted to henipaviruses such as Nipah and Hendra virus, lyssavirus and others. While predicting the next pandemic virus can be difficult, preparedness requires that we not only have a broad knowledge of these family of viruses but also have access to biocontainment facilities to conduct research and be able to develop appropriate animal models for studying disease pathogenesis and appropriate treatments. Currently, there is a scarcity of level 3 and 4 biocontainment laboratories in academic institutions. The current pandemic exposed our vulnerability in this regard. The ISNV membership might consider developing a committee to explore the possibility of developing a pandemic preparedness plan. The collective voice of the membership will likely have an impact on the decision makers.

Thank You!

On behalf of all attendees of the 17th International Symposium on NeuroVirology, we thank Dr. Michael Nonnemacher and Dr. Fred Krebs for giving us a wonderful virtual experience. The ISNV would also like to acknowledge Dr. Randy Cohrs for assisting in our virtual meeting platform. A special thank you to Joe Villaneuva, a graduate student from UC Boulder, who designed our virtual space and offered technical recommendations and assistance throughout the meeting. Gather.town provided an excellent platform to meet with colleagues, view posters, and even hit the virtual beach! We appreciate your time and expertise in facilitating the first ever virtual ISNV meeting.

A very special thank you to Sandy Weiss. Thank you for your organization, time, and commitment to ensuring the successful operation of this meeting and our society.

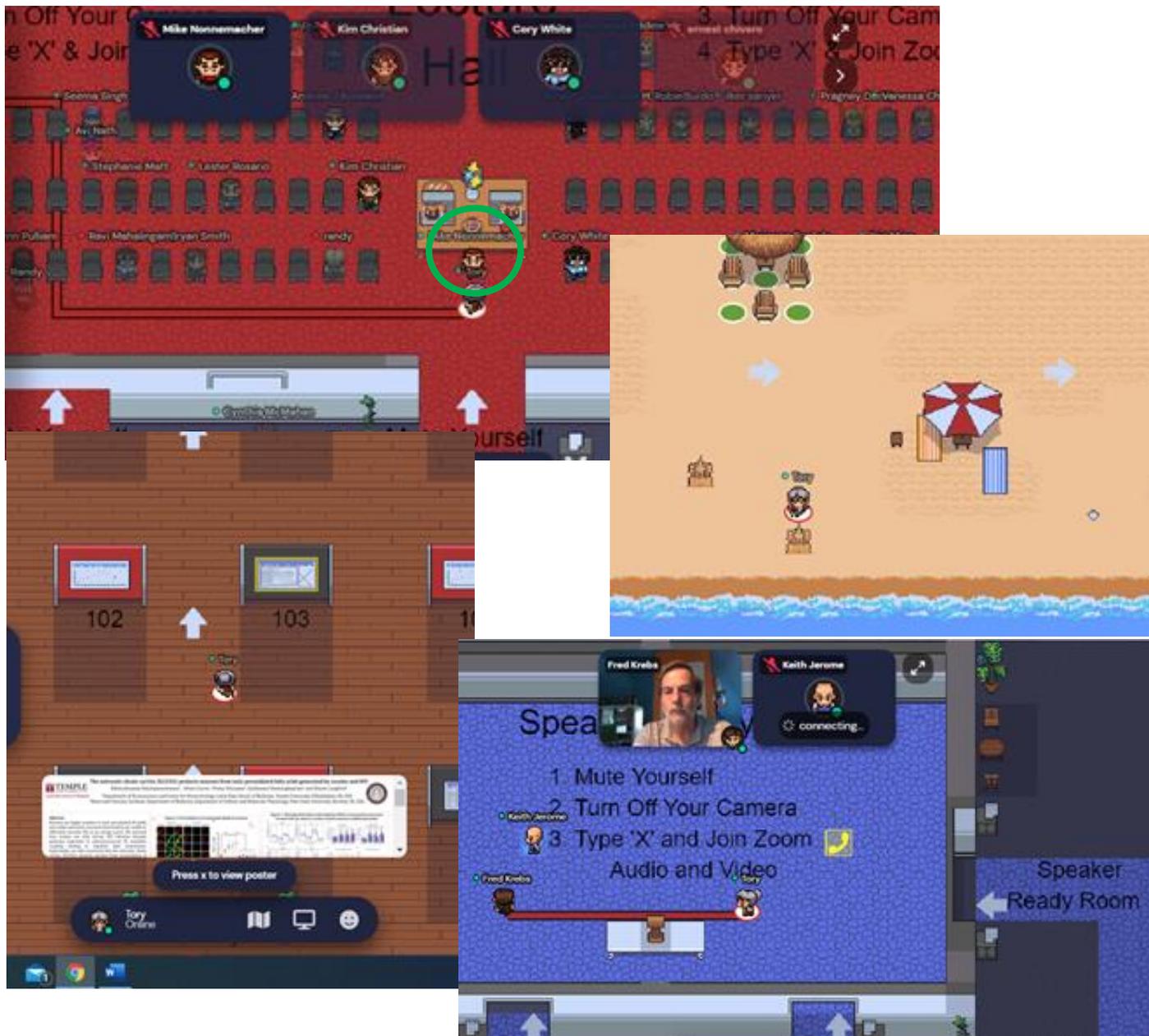


Figure 1. Screen shots from the virtual ISNV meeting. Clockwise from upper left: main lecture hall with Dr. Nonnemacher (circled in green) speaking with an attendee getting ready for a scientific session, the beach, Dr. Krebs helping a speaker prepare, and the poster session.

Unconscious Bias

By Tory P. Johnson, Ph.D.
Johns Hopkins University School of Medicine

Dr. LaMisha Hill, Director of Multicultural Affairs, Office of Diversity and Outreach at the University of California, San Francisco, San Francisco, CA, spoke with ISNV about unconscious bias. Dr. Hill explained that bias is the strong inclination of the mind or a preconceived opinion about someone or something. Our biases, and we all have them, fall into distinct categories: conscious, unconscious, and silent. These biases are rooted in our exquisitely efficient brains. Our CNS is trained during development to group and categorize stimuli to facilitate rapid and efficient decision making. This information filtering is important for our daily functioning, but it is important that we pay attention to our decision making and ensure biases do not dictate our actions. Important biases to consider include race, ethnicity, gender, age, gender identity, weight, and sexual orientation.



Image: UCSF.edu

Unconscious biases, as their name implies, are activated involuntarily. These biases can affect our understanding, actions, and decisions in either a positive or negative way. Unconscious biases form from neurocognitive associations, our individual exposures and experiences, and our socio-cultural environment. Dr. Hill gave examples of how unconscious bias influences hiring practices. For example, there was a dramatic increase in the percent of women who were hired to perform in orchestras when the auditions were blinded to the performer ([Golden and Rouse, 2000](#)).

As Dr. Hill explained, a useful way to examine unconscious bias is to ask yourself: “Who do you move towards? Who do you move away from? Why?” An important concept to consider when evaluating and learning to recognize your own unconscious biases is how your thoughts, feelings, and actions are integrated and how they influence each other.

Microaggressions are unconscious biases in action. These actions are defined as brief and commonplace verbal, behavioral or environmental slights, whether intentional or unintentional, that communicate hostile, derogatory, or negative attitudes toward stigmatized or culturally marginalized groups. There are many examples of microaggressions and they tend to cluster around several common topics (Figure 1).

Most important is how to recognize and overcome your unconscious biases. This is critical to prevent these biases from permeating your professional life. Some tips Dr. Hill provided included making judgments and evaluating people only when you are well rested, fed, and calm. Perhaps consider extending this policy to reviewing papers and grants as well. Also, Dr. Hill suggests regularly checking in with yourself and asking yourself why you are moving away or towards individuals.

ISNV is committed to raising awareness on issues of diversity and inclusion. For additional information please contact any member of the [Mentorship and Inclusion committee](#).

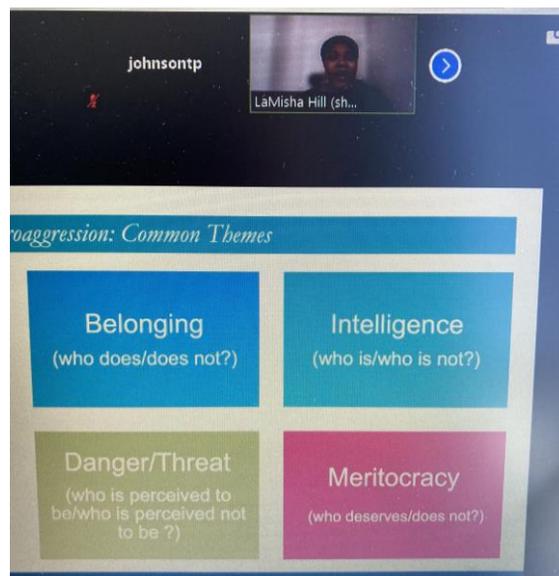


Figure 2. Screenshot of Dr. Hill describing the common themes of microaggressions.

Interested in learning more about your own unconscious biases? [Click here](#) for self-evaluation tools.

HIV Cure, aging, and co-morbidities

By Leah Rubin, PhD and Tory Johnson, PhD
Johns Hopkins University School of Medicine

The HIV Cure plenary speaker was Dr. Persaud from Johns Hopkins University School of Medicine. Dr. Persaud gave us a comprehensive overview of the HIV Cure field, including recent advancements in the pediatric and adult populations. Dr. Persaud emphasized that an HIV Cure is truly a functional cure, defined as the lack of viral rebound after the removal of antiretroviral therapy (ART). Importantly, current data shared with ISNV by Dr. Persaud demonstrate that treatment early in infection leads to long viral suppression even without continuous ART. As highlighted by Dr. Persaud, most of the Cure strategies and research in the HIV field is focused primarily on the highly heterogeneous memory CD4+ T cell reservoir.

Dr. Tricia Burdo presented development of a model to test the applicability of Cure strategies to the CNS. She provided data demonstrating the recent examination of the SHIV.D. model and its recapitulation of some hallmarks of CNS HIV pathology. Further, Dr. Burdo shared her team's plan to use this model to investigate Cure approaches involving the CNS by disabling the viral genome, via partial viral genome excision. Dr. Seung Yoo, from Johns Hopkins University School of Medicine, presented exciting data showing that inhibition of neutral sphingomyelinase 2 disrupts viral replication resulting in accumulation of viral proteins and eventual death of infected cells. This appears to allow for a persistent suppression of virus within the models studied.

Three speakers were highlighted in the comorbidities section with the common thread of providing potential pharmacological and non-pharmacological interventions for improving CNS complications in people with HIV. The first speaker was Dr. Kristine Erlandson from the University of Colorado Denver. Dr. Erlandson gave us an overview on the impact of aging in people with HIV with a primary focus on frailty which is a strong predictor of poor outcomes in this

population including falls, impairment in activities of daily living, and mortality. An emphasis was placed on the strong overlap between physical and cognitive frailty in people with HIV and that identification of people where both are present may be the most vulnerable adults with HIV. She also provided a comprehensive review of interventions for physical and cognitive frailty which included non-pharmacological interventions (exercise or physical activity) and what is known to date regarding pharmacological interventions (e.g., senolytics, testosterone, insulin-signaling/metabolic regulators). The second speaker was Dr. Johnny He from the Chicago Medical School and Rosaline Franklin University. Dr. He focused on the contribution of the $\alpha 7$ nicotinic acetylcholine receptor (nAChR) to CNS complications in HIV by way of using a number of animal models of neuroHIV including doxycycline-inducible and astrocyte-specific HIV-1 Tat transgenic mice [iTat]. This is an important area of inquiry in neuroHIV as alterations in the $\alpha 7$ -nAChR have been linked to cognitive impairment. Moreover, positive allosteric modulators (PAMs) of the $\alpha 7$ -nAChR are potential treatments for dementia, a number of neurodegenerative disorders, and conditions involving inflammation. The final speaker was Dr. Norman Haughey from Johns Hopkins University School of Medicine, who presented data from the late Dr. Ned Sacktor's clinical trial of intranasal insulin on cognitive impairment in people with HIV. In this pilot study, intranasal insulin was found to improve performance on specific cognitive domains including memory and attention. ISNV thanks the session chairs, Drs. Jeymohan Joseph and Eliezer Masliah, for an educational and inspiring session.

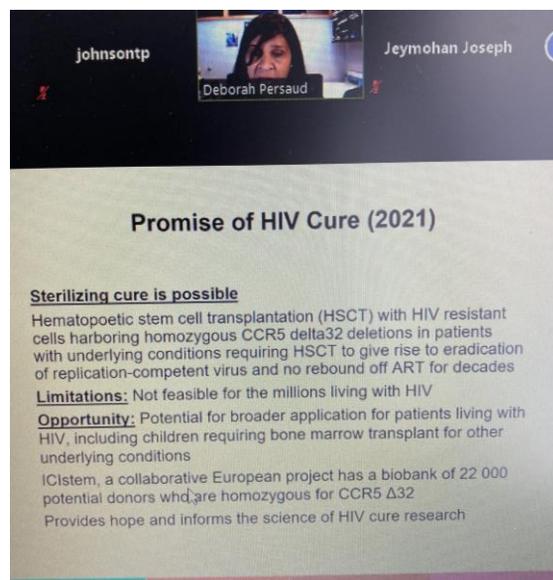


Figure 3. Screen shot during the presentation by Dr. Persaud.

Topics in Neurovirology

By Tory P Johnson, PhD

Johns Hopkins University School of Medicine

The session titled “Topics in NeuroVirology” had Dr. Keith Jerome, from The University of Washington and the Fred Hutchinson Cancer Research Center, as the plenary speaker. Dr. Jerome spoke with ISNV about genome editing of persistent herpes simplex virus -1 (HSV-1) by meganucleases. This approach is successful in reducing intact virus in vitro and in vivo. Dr. Jerome shared some important insights made during his research including that self-complementary AAV vectors are more effective delivery vehicles, that introducing double cuts into the viral genome, as opposed to a single cut, greatly increases viral reduction, and that different AAVs target different types of neurons. This last discovery, made via single cell sequencing, demonstrated that different AAV strains were specific for different groups of neurons and that efficiency of viral genome disruption could be enhanced with combinations of AAVs for meganuclease delivery.

Dr. Kimberly Christian of the University of Pennsylvania shared with ISNV an exciting in vitro model for assessing how drugs effect the developing nervous system. By using organoids Dr. Christian was able to demonstrate that the integrase inhibitor dolutegravir altered the size and structure of organoids during development in a dose dependent manner. Further, she showed that this was likely due to the integrated stress response with increases in ATF4 and p21 leading to cell cycle arrest and lack of post-mitotic neurons. This model will be critical in providing important information about drug safety, and the impact of drugs on the developing CNS, during pregnancy.

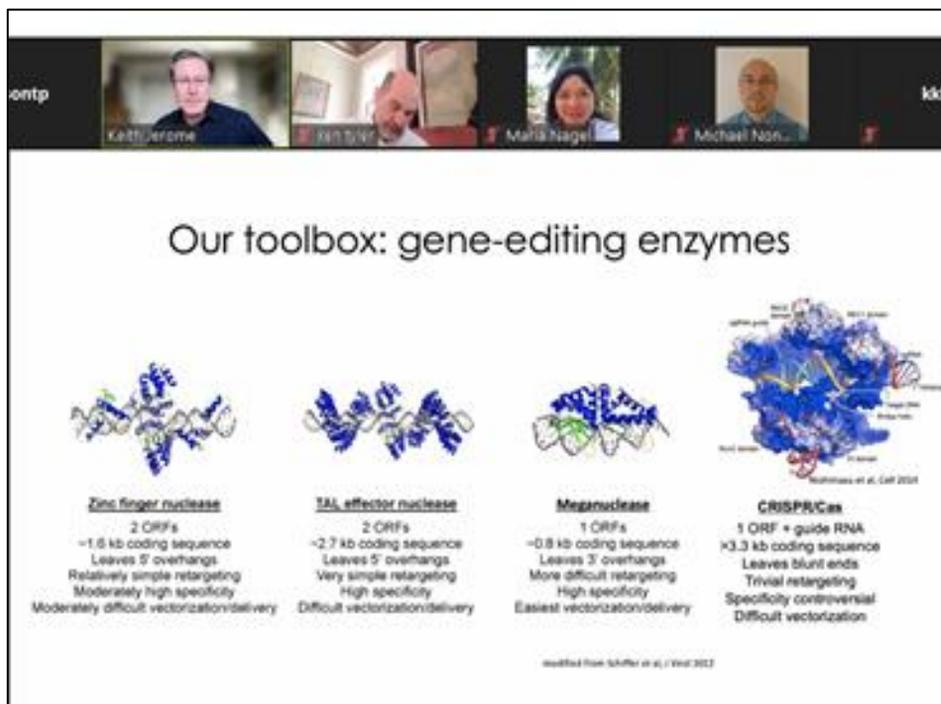


Figure 4. Screen shot during the presentation by Dr. Keith Jerome.

Drs. Randall Cohrs and Dr. Maria Nagel spoke with us about their recent work in VZV. Dr. Cohrs presented data from single cell sequencing of VZV infected human sensory neurons. He provided further evidence of alterations in cMyc and maturation markers due to VZV infection. Dr. Nagel further demonstrated that factors present in the sera and CSF of patients with VZV can induce protein aggregation, including amyloid formation. Single cell sequencing data revealed an increase in expression of amyloid associated genes and VZV infection also altered the localization and triggered amylin aggregation in a cell line model. They hypothesize

that this process of VZV induced amyloid aggregation may lead to synaptic pruning by activating microglia.

Dr. Sabrina Tan, of Beth Israel Deaconess Medical Center, presented recent work on the role of neutrophils in JC Virus infection. She demonstrated that NK cells target virally infected cells via NK activating receptors and that this component of the immune response may have an antigen specific response to JC virus. Importantly, this may result in immunological memory which could be exploited for immunotherapeutic purposes against this virus.

Investigators-In-Training

By Dianne Langford, PhD

Our ISNV Investigators-in-Training session was held on Friday June 4th and was co-chaired by Ruth Brack-Werner, Walter Royal, III, and Jay Rappaport. Eight outstanding trainees presented their recent work on viral infections. We are looking forward to following the research of these investigators in training to see new and exciting discoveries in the field.

Josh Frost from Ken Tyler's lab presented compelling in vivo data in mice infected with EV D-68 and treated with the Hep-B protease inhibitor Telaprevir. Exciting results indicated that Telaprevir improved paralysis outcomes in infected mice by lowering viral titers in early infection. The data offer promise for individuals suffering from Acute Flaccid Myelitis (AFM). Josh was awarded the Donald Gilden Pioneer award.

Nazanin Mohammadzadeh from Chris Power's lab described her studies investigating viral persistence in brain tissues from people with HIV and SIV-infected non-human primates (NHP) administered anti-retroviral therapy (ART), and in in vitro cultures of lymphocytes and microglia. Despite effective ART, RNA, total and integrated pro-viral DNA, as well as viral capsid proteins were detected in brains from both humans and NHP. These data support that eradication of the HIV brain reservoir will require approaches to augment ART efficacy in the brain of PWH. Nazanin was awarded the Richard Johnson Pioneer award.

Ben Bell from Barb Slusher's lab presented on the use of a novel inhibitor (PDDC) of the ceramide neutral sphingomyelinase 2 (nSMase2) to treat depression in HIV using the EcoHIV mouse model. Inhibiting nSMase2 in EcoHIV mice improved depressive-like behaviors. Also inhibits ceramide-dep EV biogenesis and release. These data suggest that this inhibitor may be useful to prevent spread of toxic EV cargo such as aberrant proteins including pTau. Ben was awarded the Dianne Griffin Pioneer award.

Amber Viridi from Lena Al-Harthi's lab addressed gut-brain axis in neuroHIV focusing on epithelial cells from the colon. HIV infection in NOD/SCID IL-2Rc g -/- mice showed decreased β -catenin, TJ proteins and impaired gut barrier functions. Further studies will address translocation of viral TLR ligands from the gut to CNS which may have significant impacts on HAND. Amber was awarded the Brian Wigdahl Pioneer award.

Jake Robinson from Tricia Burdo's lab discussed interactions among fibroblasts, cardiomyocytes and HIV leading to fibrosis in the heart. Findings in diastolic dysfunction in the left ventricle (LV) and remodeling in women with HIV led to investigation of the role of CCR2 in SIV-infected animals. Collagen deposition in the LV was significantly greater SIV-infected animals with increased CCR2 expressing monocytes. In addition, increased full length osteopontin in ART-naïve SIV animals that may lead to fibroblast activation. Jake was awarded the Kamel Khalili Pioneer award.

Cynthia McMahan from Bryan Smith's lab presented data describing cognitive impairments and NFL, total Tau and cytokines in CSF from 157 people with HIV (PWH) on ART for over 15 years. Although there were no significant differences in raw scores on cognitive testing, PWH showed increased numbers of impairments on the Patients Assessment of Own Functioning Inventory and higher scores on the Beck Depression Inventory. NFL, Tau and TNF- α were increased in the CSF of PWH compared to controls. Cynthia was awarded the Avindra Nath Pioneer award.

Sujata Prasad from the lab of James Lokensgard discussed how p24 antigen-specific brain resident-memory CD8+ T-cells (bTRM) may amplify responses to HIV reactivation lead to rapid release of IFN- γ , which drives subsequent interferon-stimulated gene expression in surrounding microglia. Data from mice immunized against the HIV p24 capsid protein, followed by a CNS-boost with Pr55Gag/Env virus like particles and establishment of the specific bTRM population showed IFN- γ -mediated robust expression of microglial expression of MHCII, PD-L1 and increased iNOS. These studies showed that repeated recall responses to viral Ag that modeled repeated episodes of viral reactivation culminated in prolonged reactive gliosis and exacerbated neurotoxicity. Sujata was awarded the Joseph R. Berger Pioneer award.

Investigators-In-Training

By Dianne Langford, PhD

Marianna Spatola from Galit Alter's lab presented a study describing unique brain-specific antibody signatures in people chronically infected with HIV, when CSF was compared to plasma from both ART-experienced and ART-naïve individuals. Results indicated that CSF had specific subclasses of antibodies with lower capacity to activate innate immunity functions, bind Fc- γ receptors or to neonatal Fc-R that circulates antibodies to and from the brain. ART was associated with higher polyfunctionality of plasma-antibodies compared to CSF-antibodies, suggesting a reduced effect of ART in the brain. Potential contributors include selective antibody transfer into the brain or local production by maturing B-cells under brain specific selective pressure. Marianna was awarded the Lynn Pulliam Pioneer award.

Funding Opportunities in Neuro-HIV

By Tory P. Johnson, PhD

Drs. Jeymohan Joseph and Eliezer Masliah, both from the NIH, presented several funding opportunities for Neuro-HIV related research through NIMH and NIA (see Table 1 below). These are focused on understanding the pathogenic mechanisms and genetic factors involved in the pathogenesis of HIV associated central nervous system dysfunction including cognitive, neurologic, and mental health outcomes. Additionally, work focusing on understanding the mechanisms of persistence in the CNS and therapeutic strategies to eliminate or mitigate the CNS reservoir are of high interest. The NIH is also interested in funding work that looks at the intersection of HIV, aging, and neurodegeneration, particularly with Alzheimer's disease.

Table 1. Funding mechanism for neuro-HIV.

| FOA | Title | Expiration Date | URL |
|---------------|---|--------------------|---|
| PA-20-149 | HIV Infection of the Central Nervous System (R01) | May 8, 2023 | https://grants.nih.gov/grants/guide/pa-files/PA-20-149.html |
| PA-20-151 | Eradication of HIV-1 from Central Nervous system Reservoirs (R01) | May 8, 2023 | https://grants.nih.gov/grants/guide/pa-files/PA-20-151.html |
| PA-20-308 | NIMH AIDS Research Center on Mental Health and HIV/AIDS (P30) | September 14, 2023 | https://grants.nih.gov/grants/guide/pa-files/PAR-20-308.html |
| PAR-21-068 | Multidisciplinary Studies of HIV/AIDS and Aging (R01) | January 8, 2024 | https://grants.nih.gov/grants/guide/pa-files/PAR-21-068.html |
| PAR-21-069 | Multidisciplinary Studies of HIV/AIDS and Aging (R21) | January 8, 2024 | https://grants.nih.gov/grants/guide/pa-files/par-21-069.html |
| NOT-AG-21-016 | Notice of Special Interest (NOSI): Neurological and Neurocognitive Sequelae from SARS-CoV-2 Infection and COVID-19 in Aging and Age-Related Neurodegeneration | May 8, 2023 | https://grants.nih.gov/grants/guide/notice-files/NOT-AG-21-016.html |