June 2021

SNIP

A newsletter of the Society on NeuroImmune Pharmacology

Introduction

by Ilker K. Sariyer, D.V.M., Ph.D.

Hello to SNIP family from the new Society's newsletter edited by Communication Committee. Society's newsletter is the official publication of SNIP which reports the activities of the Society, including recent and upcoming meetings and news and announcements of interest to the majority of the SNIP members. In this issue, we report the 2021 virtual workshop summary, a brief report on recent advances in COVID-19 therapy, and announcements. I want to express my special thanks to the members of the Communication Committee, Dr. Sulie L Chang, and Dr. Jean Bidlack for their edits and contributions in the preparation of the newsletter. We would like to also express our special thanks to everyone who worked hard to make a memorable virtual workshop by offering a great scientific retreat on April 9 2021.

In this issue:

President's Message

Sulie L. Chang, Ph.D., -- President

Dear SNIP members,

I hope this message finds you, your family, and loved ones healthy and well!

Since I wrote you last January, one news item most worthy to highlight is: led by our President-elect, Dr. Santosh Kumar and his organizing committee, our "2021 COVID19 Virtual Workshop" e-hosted by the University of Nebraska Medical Center on April 9th was a grand success! The presenters included SNIP members, non-member scientists, and NIH officials. This workshop demonstrated to the research communities and society at large how we have contributed to research and studies related to the pandemic by SARS CoV2 infection. The 6-hour glitch-free workshop also united the SNIPers online to share how we have overcome our personal and professional difficulties. The Brief Report of the workshop, selected papers from the workshop along with other related manuscripts from SNIP members will be published on JNIP in a special theme issue entitled "Neuroimmune Pharmacology of SARS CoV2." Dr. Kumar's outstanding leadership was one of the keys for this grand success. I have been very proud that working together we SNIPers have enabled each other to exceed our potential and collectively to rise during pandemic.

Since March 2020, the overall consideration of the current SNIP Executive Committee (EC) has been on the use of our 2019-2020 advance payments for the 26th SNIP conference in 2022, COVID19 vaccination, traveling safety and restrictions. As mentioned, last January, the Council approved the EC's decision to hold the 26th SNIP conference in 2022 at the LaLiT Hotel (https://s-nip.org/conferences) in New Delhi, India. The meeting dates are **March 2nd-5th in 2022**. However, the ongoing challenge in India has alerted us. We are monitoring the situation very closely. We will adjust the above-mentioned plans in September if necessary.

On behalf of the current SNIP EC members, we sincerely thank you for your understanding and patience while we have been trying to work out the best for SNIP. We thank Dr. Howard Gendelman and his JNIP editorial members for the special theme issue to document our 2021 virtual workshop. Last but not the least, we again thank the 26th SNIP Conference Organization Committee Chair, Dr. Pankaj Seth, and his members for their engagement in organizing this conference *during pandemic*.

Please feel free to contact me 24/7 using my email sulie.chang@shu.edu or cell phone 973 432 2073 if you may need any additional information.

2021 SNIP Covid-19 workshop summary

by Andrea D. Raymond Ph.D.

(edited by Santhi Gorantla Ph.D.)

We had a successful virtual workshop on COVID-19 related research on April 9th 2021. Presentations covering basic research, translational and clinical studies of COVID19 were shared. The workshop brought together NIH officials from NIAAA and NIDA, scientists from Neuro Immunology field to address the current and developing research involving SARS CoV2 and COVID19. It has also provided a valuable networking opportunity and set the stage for further collaboration among researchers from varying Universities. The workshop began with opening remarks by SNIP president, Dr. Sulie L. Chang followed by special talks from NIH officials Dr. Changhai Cui (NIAAA), Dr. Yu (Woody) Lin (NIDA), Dr. John Satterlee (NIDA), and Dr. Jaymohan Joseph (NIMH), and scientific presentations from researchers on topics of interest related to molecular mechanisms of acute SARS CoV2 infection in the context of co-infections, alcohol abuse, and substance use disorders. Finally, the workshop concluded with panel discussions describing the personal and professional impact of the COVID-19 pandemic.

Symposium I was on Molecular approaches to COVID-19 pathogenesis and underlying mechanisms. Dr. Booze of the University of South Carolina investigated neurological outcomes of acute SARS CoV2 infection in which she demonstrated using non-human primates that SARS CoV2 is expressed in the olfactory epithelium (OE)-sustentacular, basal stem cell, and Bowman's gland. Her work suggests that the symptoms of common "long haul" clinically termed neurological Post-acute CoV2 (nPASC) involve anxiety and depression, which may likely be reflective of SARS CoV2 in OE/pyriform cortex and potentially involved in nPASC. Dr. Cory of the University of Tennesse presented studies on cellular senescence and fibrosis in SARS CoV2 infected macrophage/fibroblast co-cultures. Dr. Dhillon of the University of Kansas presented studies on extracellular vesicles(EVs) in COVID19. She provides evidence from a cross-sectional analysis in which plasma-derived EVs from patients with varying severity of COVID-19 were compared to define a potential biomarker and examine[EV] impact on vascular injury. Dr. Gendelman of the University of Nebraska presented research on SARS CoV2 induction of pro-inflammatory human macrophage. The hypothesis is that macrophages contribute to the cytokine storm of the acute respiratory distress syndrome (ARDS) and multi-organ failure in COVID-19 patients. Dr. Mahajan of the University of Buffalo presented her work on mitochondrial dynamics in microglia treated with SARS CoV2 spike protein. She showed evidence that SARS CoV-2 induced mitochondrial -dependent intrinsic apoptotic pathways that may have implications in NeuroCOVID. Dr. Ramirez of Temple University presented the effect of SARS CoV2 spike protein on the brain endothelium and its potential role in neuroCOVID using a novel model of the neurovascular unit. Taken together, this symposium described findings for studies describing the mechanism of SARS CoV2 neurological effects. Symposium II on Therapeutic/Vaccine approaches to COVID-19 had presentations that covered the development of targeted therapeutics and vaccines for CoVID19. Dr. Byrareddy of the University of Nebraska discussed studies on small molecule entry inhibitors of SARS CoV2. The bromodomain inhibitors (iBET) were identified in silico. Dr. Ho discussed the potential of EGCG cathecins of green tea to block SARS CoV2 infection by inhibiting ACE2 binding to Spike protein. Preliminary evidence for n-linked glycosylation and palmitoyloation based anti-virals was presented by Dr Kaminski from Temple University. Targeting spike modifications by MOGCs knockout, integral for glycosylation, significantly reduces SARS CoV2 infectivity. Dr. Kevadiya of University of Nebraska, Medical Center presented preliminary finding for a new delivery vaccine platform using layer-by-layer(LBL) microparticles. LBL as a single dose can be a long-term effective vaccine delivery platform capable of easily accommodating SARS CoV2 variants. Drs. Khalsa, and Maggirwar presented on COVID19 Neuropsychiatric complications, cannabidiol (CBD), and COVID19. Dr. Blunt, an addiction psychiatrist, describes the importance of knowing the source, THC content, dosing and efficacy for CBD products in the clinic. Lastly, Dr. Pahan of Rush

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University presented preliminary findings on peptide ACE-2 interacting domain of SARS CoV2 (AIDS) to restrict the spike ACE2 – spike interaction and spike-induced inflammation in human lung cells and SARS CoV2 animal model. Overall, several approaches ranging from small molecule inhibitors, catechins, targeting Spike post translation modifications for COVID19 treatment, small peptides (AIDS) to novel vaccine delivery platforms.

Symposium III had presentations from Early Career Investigators (Pre- and Postdoctoral Fellows). As a keynote speaker of this symposium, Dr. John Satterlee of NIDA described the various funding opportunities available for various career stages from undergraduates through PI. Topical opportunities available at NIDA include single cell transcriptomics to understand substance use disorders via SCORCH program using RNA-seq data for brain regions relevant to controls, SUDs, HIV/ART and HIV/ART + SUDS. Dr. Satterlee listed a few of the "ten commandments " for writing compelling fundable grants. Lastly, he suggested subscribing to the NIH guide to learn about funding available at NIDA. Early investigators presented the following: Dr. Acharya, a postdoctoral fellow at UNMC described preliminary studies investigating SARS CoV2 and HIV co-infection in astrocyte and pericytes using multi-omics approach. He provided evidence for modest SARS CoV2 infection on these cell types and that there is a potential novel receptor for SARS CoV2 infection of pericytes. Dr. Basova of San Diego Biomedical Research Institute characterized and compared system biology of H1N1 and SARS CoV2 infection in a ferret model. H1N1 and SARS CoV2 differentially activate immune pathways. Dr. Stangis of the University of Miami examined the impact of methamphetamine and SARS CoV2 S1 spike subunit on tight junctions of human brain microvascular endothelial cells. He demonstrated a reduction in tight junctions. Dr. Torices also of the University of Miami presented studies on SARS CoV2 receptors on cells of the neurovascular unit in SARS CoV2 infection and co-infection with HIV. Overall, these early-career investigators provide interesting studies on the molecular mechanisms affected in SARS CoV2 infection on neurological cells, coinfection with HIV, and substance use.

Symposium IV was from Diversity and Inclusion SNIP Committee. The symposium started with a special talk by Dr. Jeymohan Joseph of NIMH describing the clinical observations of neurological complications of SARS CoV2 infection from the studies in China, Italy, Germany and the United States. Immune response in NeuroCOVID and pathophysiology (Brain fog, insomnia, and mood disorder) was also discussed. Taken together, studies show varied neurological impact of SARS CoV2/COVID19 and that a better understanding of the mechanisms involved is needed. Regarding funding, Dr. Joseph mentioned two notices of interest for researches significantly impacted by COVID19- K99/R00 research deadlines extended by 8 months and F- and K- awardees allow for no-cost and funded extensions. Dr. Thirumala-Devi from St. Jude presented exciting findings on innate immunity and the PANapoptosis(pyroptosis, apoptosis, and necroposis) in SARS CoV2 infection and cytokine shock syndrome, and that blockage of signaling cascade relevant to the PANaptosome may serve as a therapeutic for COVID19. Dr. Kumar discussed well-being of basic researchers – the impact on research during the COVID19 era. Generally, the mental health of college students (and postdocs) was greatly impacted and the research productivity significantly decreased overall. Dr. Kumar presented work in which he engaged his research group in COVID differentiator(COVID-Diff) study. Dr. Kumar developed a mitigation strategy and performed a COVID19 stress test after few months with his research group. Interestingly within his group, stress measurements decreased in the intervention group, demonstrating that when a crisis is beyond your control, develop an intervention for mitigation strategy and have an optimistic outlook. Lastly, symposia concluded with a *panel discussion* on personal reflection and sharing during the COVID19 era. Drs. Jean Bidlack, Sylvia Fitting, Santhi Gorantla, Cecilia Marcondes, Loyda Melendez, and Ilker Sariyer all shared their personal and professional experiences during the pandemic. The experiences included initial struggle adjusting with all teaching and meetings suddenly shifting to zoom, professional struggles of young investigators, productivity lag or loss due to lab shutdowns, curtailing the animal colonies and block in humanized mice generation which affected the experiments down the road, dealing with COVID in family, and how women with younger children were more significantly impacted. Panelists also discussed how they tried to make the best out of the situation as much as possible. Dr. Melendez turned her lab in to a resource for SARS/CoV2 testing in patients and employees. Being locked out of the lab, several investigators worked on data analysis and manuscript writing, involved students and postdocs in writing reviews, that lead to many publications.

The final remarks were given by SNIP President Dr. Chang thanking all the NIH officials, presenters, EC members and all the SNIP members for the successful virtual meeting on COVID-19.

The quest for "the holy grail" anti-SARS-CoV-2 drugs

by Rafal Kaminski, Ph.D.

There is currently no effective antiviral drug available to treat and prevent COVID- 19 (Coronavirus Disease-2019). Nevertheless, several critical data emerged from the torrent of papers and clinical trials, allowing better and more effective care of COVID-19 patients. The treatment depends on the phase and severity of the disease (PMID: 33737471). 85-90% of patients have the asymptomatic or mild- moderate disease and recover within 1-2 weeks. At this stage, like for any other viral illnesses, standard self-care applies: a lot of fluids, rest, and pain and fever relieving drugs. The patients from high-risk groups with cardiovascular disease, obesity, diabetes, hypertension, and the elderly must be monitored more closely (PMID: 33629868). Ideally, the body's immune system will stop the virus from replicating, and the patient will heal. Treatment with monoclonal antibodies was shown to cut the risk of hospitalization by two-thirds at this point if used within days of first symptoms (PMID: 33875867). Initial hopes for using antibody-rich convalescent plasma as an early treatment fall short as it failed to improve outcomes for mild to moderate disease (PMID: 34000257). Unfortunately, in 10-15% of patients, the infection progresses, and severe disease requires hospitalization. Because the blood clots develop in 17% of hospitalized patients (and 30% of ICU patients), a low prophylactic dose of anticoagulants are given on admission (PMID: 33251499, PMID: 33139519). The only FDA-approved antiviral drug for COVID-19 Remdesivir shown to cut hospital stays by several days is administered. However, it failed to improve recovery in the bigger, randomized trial (PMID: 33264556). As the blood oxygen levels drop, some patients need oxygen support. In around 30% of hospitalized patients, the disease is so severe that they require intensive care (PMID: 32649661). The hyperactive immune response starts to damage body organs leading to acute respiratory distress syndrome, and patients require mechanical ventilators and often dialysis. Anti-inflammatory corticosteroids such as dexamethasone or methylprednisone were shown to reduce mortality in the sickest patients but had adverse effects if used too early (PMID: 32678530, PMID: 32876694). Tocilizumab (Sarilumab), a monoclonal antibody against IL-6, also improved patient outcomes if combined with dexamethasone (PMID: 33933206). Additionally, treatment with convalescent plasma and monoclonal antibodies showed some mortality drop (PMID: 33974559). Results from large clinical trials, the gold standard of evidence, continue to provide verification and validation of results from pre-clinical studies. Several drugs failed to produce any improvement for the hospitalized patients with COVID-19. These include tested in WHO Solidarity trial (NCT04315948): remdesivir, hydroxychloroquine, lopinavir, interferon-beta (PMID: 33264556) and in UK Recovery trial (NCT04381936, https://www.recoverytrial.net/): azithromycin (PMID: 33545096), convalescent plasma (PMID: 34000257), again hydroxychloroquine (PMID: 33031652), lopinavir-ritonavir (PMID: 33031764). Several other drugs and regimes are currently being evaluated in clinical trials (PMID: 33632832, PMID: 33707248) with the hope of finding effective direct antiviral able to stop patients from reaching hospital and ICU. Most of them are repurposed drugs already approved to treat other viral infections (HCV, Zika, Ebola, HIV), autoimmune diseases, or cancer. They target different steps of the coronavirus life cycle. Viral entry and traffic inhibitors: camostat mesylate (PMID: 33676899), baricitinib (PMID: 33278358), Umifenovir (=Arbidol) (PMID: 33934117), hACE2 protein decoys (PMID: 33154107), and Miniprotein inhibitors (PMID: 32907861). Inhibitors of proteolytic processing of viral polyproteins: Lopinavir/Ritonavir (PMID: 33608241), Ledipasvir/Velpatsvir (PMID: 32194944), PF-07304814 (PMID: 32935104), and Boceprevir/GC376 (PMID: 32887884). Orally bioavailable nucleoside and nucleotide analogs which incorporate into RNA and block viral replication: sofosbuvir (+daclatasvir or ledipasvir, PMID: 33338232), ribavirin (PMID: 32222463), AT-527 (PMID: 33558299), molnupiravir (PMID: 32253226), and favipiravir (PMID: 33930706). Blockers of dihydroorotate dehydrogenase (DHODH), a key enzyme in the de novo pyrimidine synthesis pathway (PMID: 32754890, PMID: 33249060). Viral genome and transcripts can also be directly targeted using the CRISPR-Cas13a system, RNA-guided RNA-targeting endonuclease (PMID: 33536629). Protein synthesis inhibitors will affect both the initial translation of viral polyproteins and the production of viral structural and accessory proteins before virus assembly and packaging: eIF4Ainh zotatifin (PMID: 32353859) and eIF4Ginh. rapamycin(=sirolimus) (PMID: 33665645) and eEF1Ainh. plitidespin PMID: 33495306). The most effective way to protect individuals and to reduce the spread of pandemic are vaccinations. According to the WHO registry, there are 100 vaccines in clinical, 184 in pre-clinical development. Only a few of these vaccines are being approved for emergency use. Because of limited manufacturing capabilities and disparities in vaccine distribution, most of the world's population remains unvaccinated. Unmitigated virus spread leads to the emergence of new viral strains potentially resistant to vaccine-induced immunity. Therefore, identifying readily available and accessible direct antiviral able to block COVID-19 progression and related mortality remains a priority.

Announcements

Call for submissions to the JNIP special issue on SARS-CoV2

There is a special theme issue of JNIP in development, tied to SNIP's 2021 COVID-19 Virtual Workshop. The theme is titled "**The Neuroimmune Pharmacology of SARS-CoV-2**" with Guest Editors Drs. Sulie L. Chang and Santosh Kumar. Contributors to the theme issue can designate the "theme" when submitting manuscripts to JNIP's Editorial Manager system. Manuscripts accepted after peer review will be published immediately online in advance of the print edition.

The Cell and Immunology Core of the NIDA P30 Center of Excellence at the Center for Substance Abuse at the Lewis Katz School of Medicine at Temple University has the capability to collaborate with investigators that have samples from rodents or humans that you wish to analyze for levels of cytokines, chemokines, neuropeptides or hormones (including cortisone). The study has to have relevance to NIDA's mission of investigating substance abuse. Samples can be in blood, peritoneal fluid, saliva, cerebral spinal fluid or organ homogenates, or areas of the brain. Multiplex analysis can be performed to screen for a panel of mediators, or ELISAs can be carried out to determine levels of individual analytes. If you are interested contact Toby Eisenstein, Ph.D. at tke@temple.edu

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Postdoctoral training opportunity at Temple University Lewis Katz School of Medicine

The laboratory of Dr. Wen-Zhe Ho at Temple University is seeking a Postdoctoral Fellow to study host cell-mediated immunity against HIV infection. We focus on the following areas: **(1)** To analyze the immune and bystander cells-mediated innate immunity against HIV; **(2)** To study whether the environment factors such as drugs (opioids, methamphetamine) of abuse impair host cell innate immunity and facilitate HIV infection; **(3)** To identify novel natural products against HIV and SARS-CoV2 infection and transmission. For further information about Dr. Ho's lab, please visit: https://medicine.temple.edu/wenzhe-ho. The Ho lab is located in Medical Education Research Building (https://news.temple.edu/news/2017-08-29/lewis-katz-school- medicine-ranks-top-10-applicants) of the Temple University Lewis Katz School of Medicine.

Qualifications: The position requires that the applicant has one of the following degrees: a PhD and/or MD by the time of employment with preferred research expertise in one or more of the following areas: Molecular biology, immunology, drugs of abuse research and virology. The successful candidate should have documented success in research publications on related topics.

Appointment: The initial appointment will be for three years with the possibility of renewal for two more years. Stipend follows NIH standard rates, and the University provides a generous package of fringe benefits.

Interested applicant should send (1) resume, (2) a one-page summary of previous research experience, and (3) three letters of recommendation directly to Dr. Wen-Zhe Ho's email: wenzheho@temple.edu

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Research Scientist position at Temple University Lewis Katz School of Medicine. Department of Neuroscience will be providing comprehensive coordination of research projects and analysis related to molecular neuroscience and addictive stimulants on the brain of patients infected with the human immunodeficiency virus HIV-1. The Research Scientist will be performing biological/molecular research using techniques such as cell transfection, RT-PCR, viability assays, cell culture maintenance, immunohistochemistry, gene editing, protein analysis using biochemical techniques and bioinformatics including both RNA sequencing and electrophysiological data processing. The candidate will also be providing complex technical assistance involving microelectrode array analysis of neuronal cell function and action potential of other cell types to principal investigators in support of research activities; and managing the day-to-day research studies and general data collection.

Required Education and Experience: Ph.D. in Biology, Bioengineering/Chemical Engineering, Genetics, Biochemistry, or Molecular Biology and at least four years of experience in the field of biomedical research/molecular neuroscience. An equivalent combination of education and experience may be considered.

Interested applicant should send (1) resume, (2) a one-page summary of previous research experience, and (3) three letters of recommendation directly to Dr. Kamel Khalili's email: kamel.khalili@temple.edu