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News in NeuroVirology

Official newsletter of the
International Society for NeuroVirology
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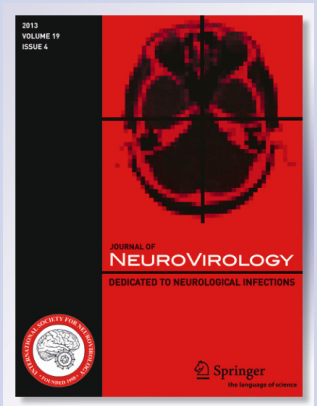

A Message from the President

By Bruce Brew

The Board and I wish to express our ongoing support for our members during this extremely difficult time. As a society we want to help each other. Please let us know if there are issues with which we can assist. The road ahead is difficult to see but hopefully that is the darkness before dawn.

ISNV 2021 Meeting Update

Details regarding the 2021 ISNV virtual meeting will be coming soon.

Navigating Unknowns

By Fergan Imbert
Doctoral Candidate, Temple University, Langford Lab

We often hear so much about how grad school makes you feel overwhelmed, sad, depressed or it “breaks your spirit”; that struggling in graduate school is normal and is some rite of passage. The COVID-19 pandemic has unfortunately reinforced some of these feelings. Well before the pandemic, there was mounting evidence that mental health among graduate students was a significant problem, with many experiencing higher rates of depression and anxiety, and fewer actually seeking out professional help. As a new student myself, the movement of classes and lab meetings to an online platform to allow for social distancing provoked a destabilizing environment in which I struggled to stay focused. On top of the isolation from social distancing and remote learning, I was experiencing the trauma of anti-Black racism and racial injustice. So, when the university made the difficult decision to halt all non-essential research, I began to experience heightened uncertainty and anxiety. When will I have access to vital resources necessary for the progression of my thesis? What does this mean for time to degree completion?

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While those feelings of anxiety and uncertainty occupied my mind and thoughts, the COVID-19 pandemic also heightened my resolve to pursue a career in neurovirology. This pandemic has highlighted the importance of research, specifically in the discipline of virology. Viruses and viral diseases represent a melding of science and medicine and has historically been at the center of some of our greatest challenges (think Smallpox) and COVID-19 is no different. The eradication of Smallpox was the result of the collaborative efforts of virologists and their contributions to our understanding of basic cellular processes and disease mechanisms. Getting to the other side of the pandemic and living in what is sure to become our "new normal", will require much more than social distancing and face coverings. It's going to take the collaborative work of research scientist and graduate students, who are the key to scientific productivity.

Recognizing the importance of sustained communication for collaborations zooming and socially distanced meetings have become the new normal to support our research continuity. Fortunately, we have found an effective way of balancing what we could control during the COVID-19 pandemic, while never losing sight of the long-term goals of our lab. These virtual dialogues provide a platform for each of us whether in lab or in class, to think creatively about the nature of our work, and it has added a level of accountability to our role as researchers (**Figure 1)**.

Uncertainty is a natural, unavoidable part of life. As the coronavirus pandemic has demonstrated, everything can change very quickly and can be extremely unpredictable. With an increasing human population, globalization, and a changing climate, the emergence of a novel infectious agent is likely. While many of us use worrying as a coping mechanism, it only leads to a false sense of control on uncontrollable events. Instead, focusing on the things we can control is a much healthier approach to coping with uncertainty. With labs slowly re-opening, researchers can return to the crucial work of identifying new infectious agents and understanding the underlying pathogenesis of associated diseases. Together, the work can provide promising ways of managing future pandemics and new ways of navigating uncertainty.

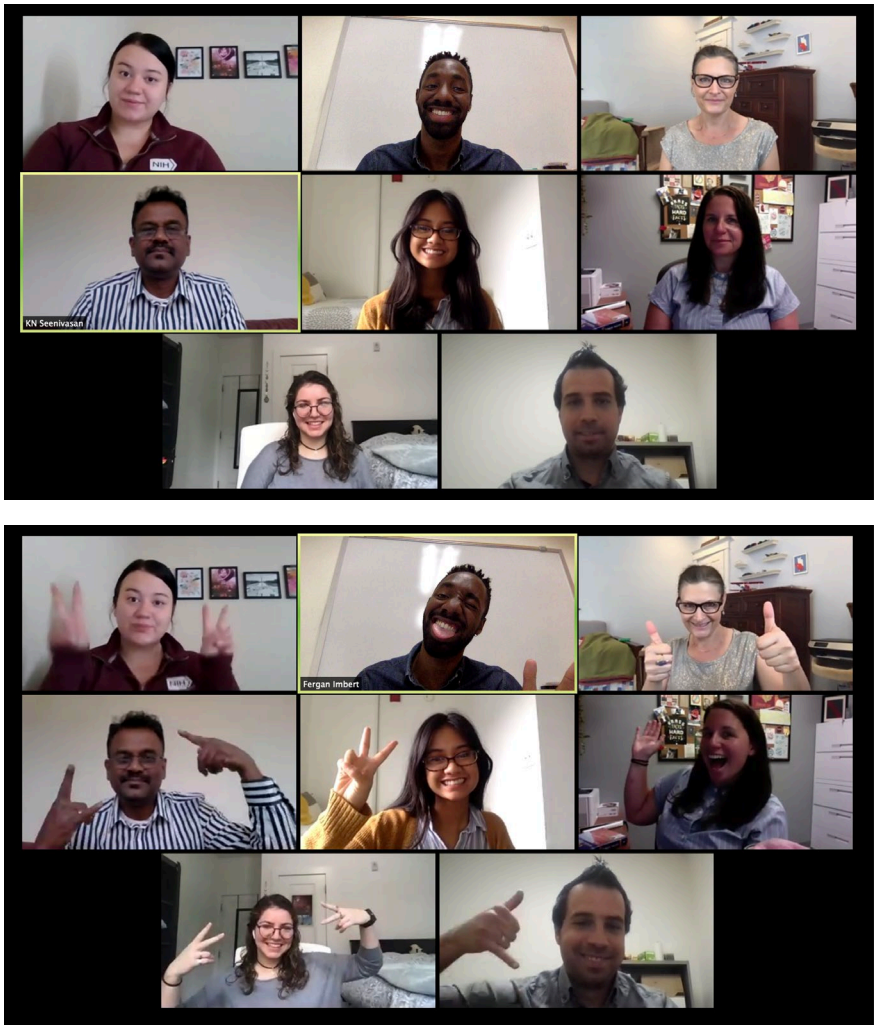

Figure 1. Well adjusted to change. A screen shot of the online Langford Lab group meeting shows the team having fun while keeping safe through social distancing.

Acute Flaccid Myelitis: what to watch for in 2020 and beyond

By Eileen Yee, MD, Tory P. Johnson, PhD and Sarah Kidd, MD
The Centers for Disease Control and Johns Hopkins University School of Medicine

What is AFM: Acute flaccid myelitis (AFM) is an uncommon but serious neurological disease. Most often, patients present at an emergency room with rapid onset of flaccid paralysis or weakness in one or more limbs, with proximal strength more often affected than distal strength. Magnetic resonance imaging (MRI) of the spinal cord reveals longitudinal lesions predominantly in the gray matter (1). AFM has occurred as a biennial outbreak in the United States since 2014.

AFM has been called a new "polio-like" illness since the initial clinical presentation can mimic the poliomyelitis associated with poliovirus infection. Poliomyelitis caused by poliovirus has been eliminated in the US since 1979 due to the successful polio vaccination program. After clusters of acute limb weakness in previously healthy children with no evidence of poliovirus infection was reported from California and Colorado in 2014, the term AFM was adopted to distinguish itself from poliomyelitis caused by poliovirus. After these initial cases were reported, CDC began national surveillance for AFM. CDC continues to remain vigilant for polio and all stool specimens sent to CDC from AFM cases are tested for poliovirus; all have been negative to date.

Who is impacted by AFM: This is a disease that predominantly impacts children. A recent analysis of confirmed cases from 2018 showed that 94% of all patients were less than 18 and the median age of patients was 5.3 years (2). Both males and females and all races can develop AFM.

When and where does AFM occur: Since 2014, reported cases of AFM in the US have peaked during August to November of every other year, with an increase in cases in 2014, 2016, and 2018 (**Figure 2**). In 2015 and 2017, there were far fewer cases confirmed. There were 46 cases of confirmed AFM reported in 2019 and, as of July 31, 2020*, there have been 16 confirmed AFM cases reported during 2020. Based on the previous pattern in the United States, there is concern that another peak of AFM will occur during the fall of 2020. AFM cases have been reported throughout the United States and from nearly all regions around the globe.

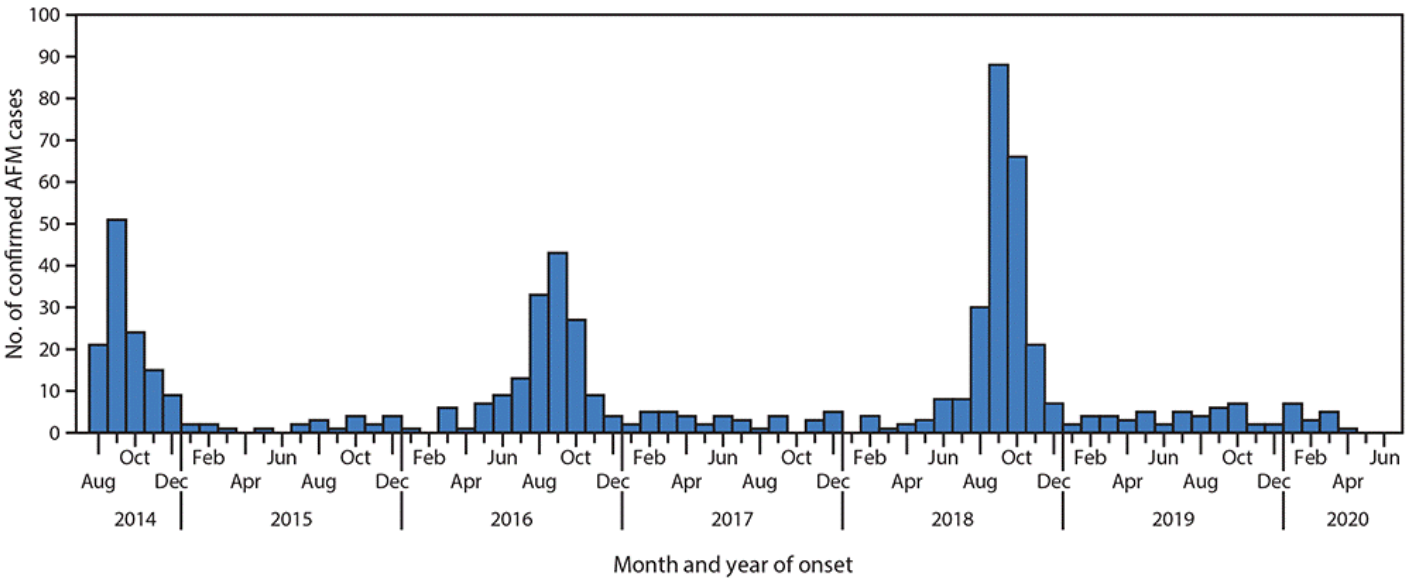

Figure 2. Confirmed cases of acute flaccid myelitis reported to CDC (N = 633), by month and year of onset in the United States, August 1, 2014–July 31, 2020. Reprinted from (2),
DOI: http://dx.doi.org/10.15585/mmwr.mm6931e3

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What causes AFM: Multiple viruses are associated with AFM in a small percentage of infected patients, including enteroviruses, flaviviruses, and adenoviruses. However, AFM that has been observed in a biennial pattern since 2014 is likely caused by non-polio enteroviruses, such as EV-D68 and EV-A71. Most patients (92%) reported either a febrile illness, upper respiratory infection, or both prior to the onset of AFM in 2018 (2).

What to look for in patients: Rapid onset of limb weakness in one or more extremity with decreased deep tendon reflexes, especially when accompanied by neck or back pain and/or a recent history of a febrile viral illness should heighten suspicion of AFM. Often the limb weakness is asymmetric, and the upper extremities are more commonly affected than lower extremities. Cranial nerve abnormalities may also be present such as facial or eyelid drooping, difficulty swallowing or speaking, or hoarse or weak cry. It is important to recognize AFM quickly as patients can rapidly progress to respiratory failure. Almost all (98%) of AFM cases in 2018 were hospitalized, 54% were admitted to the ICU, and 23% patients required endotracheal intubation and mechanical ventilation (2).

Prompt hospitalization is needed for suspected patients with AFM. MRI of the brain and spinal cord with the highest Tesla scan available should be ordered. Biological samples for testing should also be collected as soon as possible to increase the probability of pathogen detection. It is important to increase awareness about AFM and to educate colleagues and those outside of the neurology and neurovirology fields as front-line clinicians may encounter these patients first.

How to report a suspected case of AFM: CDC conducts surveillance for AFM to better understand disease burden and trends over time by gathering data from reported cases in the US. Clinicians play a vital role in initiating this reporting. All patients suspected to have AFM should be reported to the local or state health department as procedures have been put into place to readily assist clinicians in the reporting and collection of specimens onto CDC. For more information, see: https://www.cdc.gov/acute-flaccid-myelitis/hcp/clinicians-health-departments.html

What next: During the last five years of AFM surveillance, CDC and the scientific community have grown in our understanding of AFM. However, many questions have remained unanswered.
For example:

- What changed in 2014 and caused the apparent increase in enterovirus-associated, and specifically EV-D68-associated, AFM?
- Will the periodicity continue every other year?
- How will the COVID-19 pandemic and social distancing measures affect trends in AFM?
- What is the fundamental pathophysiology of non-polio enterovirus mediated AFM?
- What host factors (i.e. genetics or other risk factors) influence who gets AFM after EV infection?
- What are the B and T cell response/epitopes in EV-mediated AFM?
- And why is the predominance of AFM in children?
- What is the role of direct viral infection of cells versus immune mediated damage?
- What is the mechanism of viral spread to the CNS?
- Why are the anterior horn cells targeted by EV-D68?
- Could other cells (interneurons, myocytes) also be infected?
- Are mutations in EV-D68 over time antigenically significant?
- How narrow is the timing of therapeutic window for treating AFM?

With clearer understanding of the pathophysiology of AFM, targeted diagnostics, treatments and preventive measures can be implemented.

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Acute Flaccid Myelitis: what to watch for in 2020 and beyond

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CDC has been actively engaged and working with other researchers to learn more about AFM. Currently, two ongoing studies that neurovirologists should be aware of are the NIH Natural History Study, which is a collaboration between CDC, AFM Working Group, and the Collaborative Antiviral Study Group. This study seeks to enroll children with suspected AFM and their households in the US, Canada, and in other countries to better characterize the epidemiology and natural history of AFM. The study will also collect specimens for a bio-repository to be used for future research. For more information: https://www.uab.edu/medicine/peds/casg/current-studies/acute-flaccid-myelitis-study.

CDC has also contracted out to GDIT/McKing Consulting Group to enhance specimen collection for the bio-repository at US institutions not participating in the NIH Natural History Study. For further information about this, please contact: 1-855-874-6912 or AFMProject@secure.mcking.com. Since AFM is relatively uncommon and cases are distributed throughout the US, the biorepository will be invaluable for future AFM research.

For other CDC AFM resources, please see: https://www.cdc.gov/acute-flaccid-myelitis/index.html and for the latest AFM case counts *: https://www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html

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Peter Kennedy Receives Prestigious Royal Medal

By Lynn Pulliam

Image credit: EUSTM

Founder ISNV member, former past president and recent Pioneer Award recipient Professor Peter Kennedy, was presented in October 2020 with the prestigious Royal Medal from the Royal Society of Edinburgh (RSE), Scotland's National Academy, in recognition of his work in developing neural cell markers and improved methods of treating sleeping sickness and different neurotropic viruses. The RSE Royal Medal, awarded on the authority of Her Majesty The Queen, recognizes Professor Kennedy's pioneering work in distinguishing the major human brain cell types that has paved the way to significant advances in the treatment of neurological diseases and infections, as well as identification of a novel therapy for African trypanosomiasis.

The ISNV community extends its congratulations to Dr. Kennedy for receiving this most prestigious honor.

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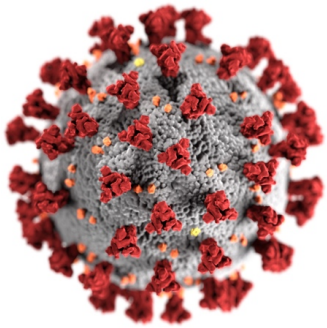
COVID-19 Virtual Biobank

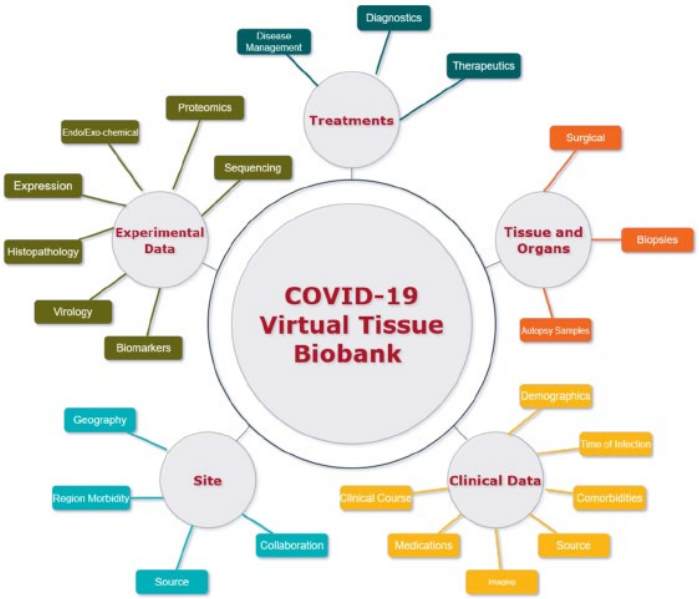
By Dr. Rajnish S. Dave

Dr. Howard Fox and his team (Dr. Rajnish S. Dave and Ms. Ashley O. Hanson) have launched the COVID-19 Virtual Biobank (https://covidbank.unmc.edu/) at the University of Nebraska Medical Center in Omaha, Nebraska in response to the ongoing pandemic. The purpose of the project is to create a network of tissue and data repositories to connect investigators (researchers, clinicians, hospitalists, pathologists and biobankers). A virtual biobank is an electronic database of biological specimens and other related information. As such it can bring together a widely dispersed collection of biospecimens and associated data in one location. This is accessible, through a secure interface, independent of where the specimens are stored. Investigators can then obtain access to more collaborators and specimens with accurate metadata, giving power and rigor to their study. Donors (patients/subjects) benefit as they are assured that samples are valued and will be used for high quality studies as opposed to being stored and archived. Researchers benefit by obtaining high quality specimens and performing well-powered studies. Collaborative teams form and share knowledge, expertise, and data, maximizing biomedical progress.

Dr. Fox's team is experienced in setting up and running such a virtual biobank in our role as the Data Coordinating Center (DCC) for the National NeuroAIDS Tissue Consortium (NNTC). While starting as a brain bank, they have evolved into a comprehensive source of biospecimens and data from a longitudinal cohort. They maintain a centralized database containing clinical data, experimental data, and specimen information, accessible by a secure-access web portal which includes user mechanisms for querying the database. A major focus and role of the NNTC-DCC is to facilitate collaboration between stakeholders, which in addition to neuroHIV research community now includes those working on HIV reservoirs and cure efforts.



A particular interest of Dr. Fox's team is the effects of COVID-19 on the nervous system. These were found in over one-third of Wuhan patients. Here in the US, central nervous system involvement is seen in approximately one-fourth of patients, including young adults with severe sequelae such as stroke. Peripheral nervous system disorders such as Guillain–Barré syndrome are also present. Linking together investigators with specimens and data from such patients will enable needed work to help prevent and treat such complications. Others will have their own clinical and research interests, and through the virtual biobank Dr. Fox aims to facilitate this process. For further information, please visit https://covidbank.unmc.edu/ or contact us at hfox@unmc.edu.



On our desks

ISNV Communications Committee

Here are some of the papers we are reading right now. Click the link to access the paper directly. Do you have a paper of interest to share? Message us and we will share it with the ISNV community.

Image credit: ISNV

Lynn Pulliam: This Letter shows that SARS-CoV-2 infects both human induced pluripotent stem cell-derived neural progenitor cells in neurospheres as well as more mature brain organoids and releases infectious virus. Immunostaining showed that SARS-CoV-2 infects neurons and neural progenitor cells in brain organoids. This article is important since an earlier report suggested that SARS-CoV-2 might have a somewhat restricted infection of neurons. This article confirms neural progenitor and more mature neuronal infection and release of virus.

A second article has a more extensive study of SARS-CoV-2 infection of human-induced pluripotent stem cells and region-specific brain organoids. Choroid plexus organoids had a productive viral infection that leads to cell death. Detailed transcriptional dysregulation was shown.

Together, these two papers prove SARS-CoV-2 neuronal infection and disruption and are important for neurological follow-up studies on people recovering from COVID-19.

Rajnish Dave: An autopsy case report is one of the earlier studies from USA that describes the neuropathology of COVID-19. The authors observed an acute disseminated encephalomyelitis (ADEM) like pathology. The spectrum of neuropathological findings included neocortical infarcts, focal hemorrhagic white matter lesions, and discrete foci of acute axonal injury with associated myelin loss. Several types of lesions identified in corpus callosum genu and subcortical white matter could potentially contribute to neurological manifestations of COVID-19 patients.

Image credit: UNMC

Image credit: Drexel University

Michael Nonnemacher: As SARS-CoV-2 has emerged into the world, it became necessary to understand its mode of entry into host cells. This paper was one of the earliest to confirm angiotensin-converting enzyme 2 (ACE2) as the receptor for SARS-CoV-2. It also showed that the cellular protease TMPRSS2 was used to prime the viral spike (S) glycoprotein for entry. In the process of this research it also demonstrated SARS-CoV-2 (i) did not use the known coronavirus receptors APN and DDP4 and (ii) that antibodies to SARS-CoV might cross-neutralize SARS-CoV-2.

Molecular mechanisms involved in HIV-1 Tat and astrocyte driven amyloidogenesis

By Dr. Rajnish S. Dave

One of the neuropathological findings in people living with human immunodeficiency virus (PLWH) is the presence of amyloid β (Aβ) plaques in the brain (1). Both aging and prolonged combined antiretroviral treatment (cART) may result in accumulation of Aβ plaques. The aging PLWH population also experiences neurodegenerative processes and more rapid cognitive impairment than their younger counterparts (2). As such, HIV-associated neurocognitive disorder (HAND) and Alzheimer's disease (AD)-like pathologies frequently occur in aging PLWH.

Amyloid proteins are mostly produced by neurons and form extracellular Aβ plaques. Reactive astrocytes surround and phagocytose Aβ plaques and secrete proinflammatory factors. Thus, in addition to neurons, astrocytes play a role in amyloidogenesis (3). HIV transactivator of transcription (Tat) protein also drives amyloidogenesis and eventually Aβ plaque formation via direct and indirect mechanisms (4). For example, Tat can bind to the Aβ fibrils and increase β-sheet formation, as well as, lateral aggregation into thick multifibrillar structures (4). Tat can also promote amyloidogenesis by disruption of the endo-lysosome in neurons (5).

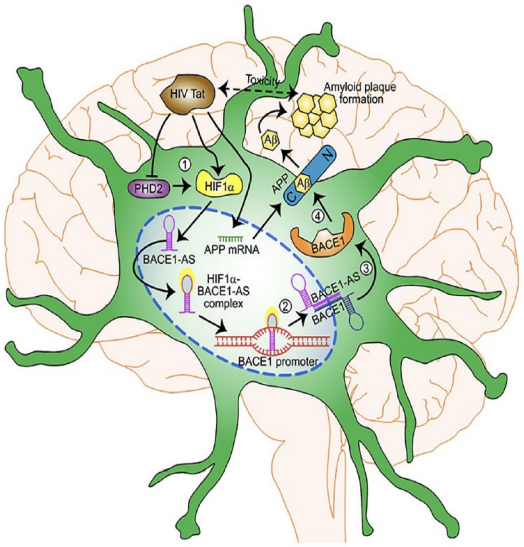


Figure 3: **HIV-1 Tat–induced astrocytic amyloidosis.** The proposed mechanism underlying Tat-induced astrocytic amyloidosis, includes 1) increased expression and accumulation of HIF-1α in response to TAT exposure, 2) induction of BACE1 transcription by HIF-1α–lncRNA BACE1-AS complex 3) stabilization of BACE1 mRNA by BACE1-AS, 4) increased translation of BACE-1. Additionally, Tat upregulated APP is cleaved by BACE1 and released as extracellular Aβ. Eventually, this extracellular protein is expected to lead to amyloid plaque formation, (Reprinted from Sil *et al., PLOS BIOLOGY PLoS Biol. 2020;18(5):e3000660.*

A recent study by Sil et al in PLOS BIOLOGY identified indirect mechanisms of Tat driven amyloidogenesis in astrocytes. Authors proposed a pathway that may contribute to AD-like pathology in HIV infections (6). They observed brain region specific upregulation of amyloid precursor protein (APP) and Aβ (40 and 42) in astrocytes from SIV-infected rhesus macaques and HIV-infected human brain tissues. Increased expression of β-site cleaving enzyme (BACE1), APP and Aβ in human primary astrocytes was also observed. Based on these observations, Sil et al. proposed a novel mechanism of astrocytic amyloidogenesis in the context of HIV infection. HIV Tat exposure upregulated two key components of the proposed amyloidogenesis pathway, hypoxia-inducible factor (HIF-1α) and APP. Upregulation of HIF-1α triggered the HIF-1α/lncRNA BACE1-AS pathway, which subsequently triggered 1) accumulation of BACE-1, 2) cleavage of APP and 3) release of Aβ (**Figure 3**).

The impact of Tat on astrocytic amyloidogenesis is likely amplified by its action at more than one point in the proposed pathway. However, Tat could also further intensity Aβ plaque formation via direct mechanisms (4). Whether the HIF-1α/lncRNA BACE1-AS pathway could be targeted for adjunctive therapies remains to be determined.

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