Better treatments, better lives

Professor Kelly Jordan-Sciutto discusses the centrality of collaboration to her work, as well as emphasising the need for more research on HIV-associated dementia, revealing hurdles she has encountered in terms of funding.

As the most common form among young adults, do you think there is enough research surrounding HIV-associated dementia (HAD)?

With the current state of National Institutes of Health (NIH) funding in the US, it seems there is less support than is needed to address key questions in the field at this time. Significant research efforts in other countries seem to have suffered a similar plight. It is difficult to discern a change in emphasis from an overall decline in funding. However, I do believe that this aspect of neurodegenerative diseases is overlooked, partly because patients with HIV have a treatment, albeit an imperfect one, and partly because it represents a small market share for companies. When there was a big outcry for drugs to treat people with HIV, a lot of emphasis was placed on research in this area, as there should be. While it is important to continue studies that may lead to eradication of the virus or a vaccine, it is shortsighted to forget the 34 million people in the world with HIV, who will be dependent on combinational antiretroviral therapy (cART) for the rest of their lives and subject to substantial side effects. Of course, cART is a great thing for patients and I don’t want to give the impression that it wasn’t a great pharmacologic achievement. It permits people to live with HIV. However, we can’t give up on finding better treatments or helping patients live better lives in the meantime.

I also feel that we could learn a lot about treating other neurodegenerative diseases by studying HIV-associated neurocognitive disorders (HANDs). This is a population of people we know are at risk for developing cognitive decline. Given the common mechanisms of disease – inflammation, oxidative stress, integrated stress response (ISR) induction – findings that help this population may be translatable to other neurodegenerative diseases.

What is entailed by your roles as Professor and Chair of Pathology at the University of Pennsylvania? Are these positions complementary?

As Professor of Pathology, I perform three key functions: leading an extramurally funded research team to investigate in my area of scholarship; teaching pathology at the School of Dental Medicine; and serving on school and university committees. I am particularly active on committees that serve to increase diversity and equity at the University. I also participate in graduate student education through my activities in the Neuroscience Graduate Group, of which I am vice chair; the Pharmacology Graduate Group; and the Cell and Molecular Graduate Group.

As Chair of Pathology, I oversee the administration of the faculty within the Department of Pathology and direct the Pathology course for dental students. These activities are complementary – I direct the course in which I teach and coordinate the other members of the Department to teach within the course. I also oversee the research mission of the Department and faculty evaluations, recruitment, appointments and promotions.

How are therapeutic interventions for Alzheimer’s disease (AD) most effectively tested?

I think determining the usefulness of a therapeutic intervention would potentially be easier in the HIV population compared with a population-based study of ageing individuals, as current diagnosis of AD occurs too late for interventions to show efficacy. In HIV, treating a large group of patients and testing efficacy could be done preventively. This seems to be overlooked by the pharmaceutical industry as it views the HIV population as too small a market.

What importance do you accord to collaboration?

Collaboration is crucial to answering interdisciplinary questions and it has been key to my research programme – I have several longstanding partnerships that have been instrumental to my research programme. I view collaboration as an extremely important part of research; it increases the impact of our work and allows us to ask the most critical and pertinent questions.

Do you have any exciting future plans in the pipeline?

While the role of IRS and antiretroviral therapy toxicity has been a focus of my laboratory for the past six to seven years, I have a longstanding project looking at cell cycle protein function in the central nervous system. Our data on this project have demonstrated that E2F1 has interesting and unexpected roles in neurite outgrowth and neuron function. Even more exciting, E2F1 seems to be functioning through a mechanism that has not been previously described. While much more work needs to be done to show this definitively, we are highly enthusiastic about these findings and hope that they shed further light onto the damage seen in neurodegenerative diseases and how it can be reversed.
**HIV IS A** slowly replicating retrovirus that is the causative agent of AIDS, in which the immune system progressively fails and the patient eventually succumbs to an opportunistic infection or disease. Despite its status as a debilitating condition, HIV is no longer considered a death sentence to those infected, largely due to effective treatments that suppress the virus, halting its progress and preventing associated symptoms. The treatment used is known as combinatorial antiretroviral therapy (cART) and involves the use of nucleoside reverse transcriptase inhibitors (NRTIs) and either their non-nucleoside counterparts (nNRTIs) or protease inhibitors (PIs). These treatments take advantage of different mechanisms to prevent the retrovirus from replicating – the former provides nucleosides that do not have a 3'-hydroxyl group, which is critical for further DNA synthesis, while the latter two target key proteins and inhibit their action. The use of multiple mechanisms ensures the efficacy of viral suppression.

**MYSTERIOUS MECHANISMS**

One of the hallmarks of HIV infection is the development of HIV-associated neurocognitive disorders (HANDs) such as encephalopathy and dementia. These conditions are thought to be directly caused by the retroviral infection of macrophages and microglia in the brain and their subsequent dysfunction, rather than being a consequence of an opportunistic infection or disease. Available treatments allow those affected by HIV to live much longer. Prior to cART, those who developed HIV-associated dementia (HAD) were unlikely to live more than six months from diagnosis. These drugs are known to reduce the development of severe forms of HANDs, but carry significant side effects including increased risks of atherogenesis, metabolic syndrome and diabetes, as well as lesser forms of HANDs.

Although these associated diseases have long been recognised, relatively little is known about their mechanisms of action, largely due to a lack of adequate small animal HIV models for study.

**NEW DEVELOPMENTS**

Professor Kelly Jordan-Sciutto at the University of Pennsylvania, USA, hopes to glean insight into these poorly understood conditions through elucidation of these mechanisms of neuronal damage in response to neuroinflammation caused by HIV. Her group considers neural cell responses to inflammation in relation to disease progression, the integrated stress response, the endogenous antioxidant response and cell cycle protein signalling. These are all thought to be involved in the development of HANDs, but it is unknown precisely how their constituent pathways contribute to the disease.

One of the researchers’ main methodologies is the use of in vitro cultures consisting of primary rat neuroglial tissue that has been treated with supernatant produced by infected macrophages from human donors. This enables the group to examine the effect of these infected macrophages on otherwise healthy neurons. Additionally, they conduct behavioural studies in which the effects of modification or removal of functionally-relevant genes are examined to better understand their function. The team also analyses patient tissues using quadruple label immunofluorescent laser confocal microscopy, in addition to similar studies in macaque models in collaboration with the groups at Johns Hopkins University, the University of Pittsburgh, and Tulane National Primate Center.

The group aims to determine biochemical pathways by understanding how specific disease-related proteins interact with DNA and RNA, as well as other proteins, and therefore employs a wide range of techniques including western blots, real-time polymerase chain reaction (PCR),

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**HANTS on research**

Remaining challenges in treating those affected by HIV are related to neurocognitive disorders associated with disease development, even in those who have received treatment. Ongoing research at the University of Pennsylvania is considering new approaches and developing novel therapies to overcome these barriers.

Simian models exist but are costly and challenging, and current methods of detecting viral components in patients and autopsy tissue use indirect surrogate markers. Observations of glial dysfunction, synaptic and dendritic damage and neuronal death have led to the hypothesis that pathogenic inflammation is a primary factor in HAND development.

Immunofluorescent staining for Binding Protein (BiP; green) is increased in neurons (MAP2; red) of the cortex of patients with HIV-associated neurocognitive disorder (HAND; bottom row) as compared to Neurocognitively Normal, age-matched control brain (NcN; top row). Nuclei are labeled blue (DAPI). A merged image of all three fluorescent markers is shown in column four. Images captured by laser confocal microscopy. © Kathryn A Lindl, PhD and Cagla Akay, MD

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EFFECTS OF THE INTEGRATED STRESS RESPONSE IN HIV-ASSOCIATED DEMENTIA

OBJECTIVES

To determine which aspects of the integrated stress response (ISR) pathway are protective in a neuroinflammatory state and therefore potentially a neuroprotective target to stimulate in disease, and which aspects of this pathway are detrimental – leading to neurodegenerative disease – and potentially a target to inhibit.

KEY COLLABORATORS

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PROFESSOR KELLY JORDAN-SCIUTTO
received her PhD in Biochemistry and Molecular Biology from Thomas Jefferson University in 1996. She then pursued her postdoctoral training in the division of Neuropathology with Dr Robert Bowser and then Dr Clayton Wiley. During the latter, she established an independent research programme assessing molecular mechanisms of neuronal damage and loss in response to neuroinflammation in patients infected with HIV. In 2001, Jordan-Sciutto joined the faculty of the University of Pennsylvania School of Dental Medicine, where she is currently Professor and Chair of Pathology.

affinity chromatography, immunofluorescent labelling and imaging in primary neurons.

THE INTEGRATED STRESS RESPONSE

One particular area of focus for Jordan-Sciutto is the integrated stress response (ISR) – a three-pronged signalling cascade that influences translation, transcription and splicing of a wide range of genes. The three branches of this cascade are initiated by different proteins – protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme-1α (IRE1α) and activating transcription factor 6 (ATF6). Jordan-Sciutto’s work dissects these pathways and examines their role in the disease state. Through understanding which aspects are protective and which are detrimental, she hopes to find potential therapeutic targets whose activation or inhibition could reduce or prevent neuronal death and damage. This approach has already generated important results, finding the PERK pathway to exert both neuroprotective and detrimental effects through different downstream factors. By activating the endogenous antioxidant response, the PERK pathway performs a neuroprotective role, while activation of beta secretease, a precursor to amyloid beta, is thought to exacerbate problems of protein misfolding and pathological accumulation, similar to that characteristic of Alzheimer’s disease (AD).

Jordan-Sciutto has followed this up with further study of PIs, which shows two members of this class of drugs to activate the PERK pathway and thereby induce the production of beta secretase in an ISR-dependent manner. “These studies may explain our finding that HIV-positive patients have increased levels of intracellular amyloid precursor protein beta-oligomers,” she explains. PIs were additionally found to prevent oligodendrocyte precursors from differentiating, adding a new facet to observed changes in white matter in HAND patients, which was previously believed to be secondary to neuronal loss.

LOOKING FORWARD

Jordan-Sciutto’s future work hopes to investigate this latter finding more thoroughly, by observing the effects of HIV drugs on remyelination in vivo. This is a matter of great importance to HIV patients taking CART, because many continue to lose white matter despite effective HIV suppression.

Next steps include the development of a small animal model of the disease. This is required if findings in cell cultures are to be effectively translated into treatments for the side effects of antiretroviral therapy. Once developed, the team will search for strategies to prevent neuronal death and synaptic damage, while also combating the challenge posed by oligodendrocyte differentiation and myelin formation. This carries wider implications, not only by furthering basic scientific knowledge of the ISR in different cell types, but also because overlap between this field and that of conditions such as AD may provide unexpected insights into neurodegenerative disease.