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Commentary: Animal Models of NeuroAIDS

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Animal models facilitate a deeper understanding of disease while at the same time eliminating any harm to humans. The idea is to enable important breakthroughs in our understanding of pathogenesis, improve diagnostics, and provide new targets for prevention and treatment of disease. The consequences of central nervous system (CNS) HIV infection (referred to as neuroAIDS) and strategies for disease prevention and treatment remain of critical importance for the global HIV/AIDS pandemic. While combination antiretroviral therapy (CART) has markedly reduced disease morbidity and mortality including the severe cognitive and motor dysfunctions or HIV-associated dementia, HIV-associated neurocognitive disorders (HAND) as well as sensory neuropathies remain common in the CART era, with up to half of HIV-1 patients affected (Heaton et al., 2011; Elliott et al., 2012).

To further stimulate discussion and facilitate studies in neuroAIDS, we organized the "Animal Models for NeuroAIDS" research symposium that was held March 24, 2012 at the University of Nebraska Medical Center, Omaha, Nebr. The twelve invited speakers covered a variety of current models and their applications in therapy, diagnostics, pathogenesis, and future needs of HAND followed by a panel discussion. Scientists from 40 institutions attended in person or through the Internet. In the spirit of encouraging further discussion and disseminating the meeting's presentations, the *Journal of Neuroimmune Pharmacology* features papers on animal models of neuroAIDS. The ten papers include reviews as well as original experimental contributions.

Mouse and rat models are commonly used in study, as they are invaluable in reflecting the immunology, neurobiology, virology, and disease pathogenesis of human disease. Investigations of virus-induced neurotoxicity, leukocyte migration, target cell infection, antiretroviral, and adjunctive therapies are reflected in those models. One mainstay of modeling HIV infection of the brain has been the creation of transgenic rodents expressing viral proteins in the brain. Expression of the HIV coat protein gp120 in the CNS of mice by astrocytes was the first such model (Toggas et al., 1994). Maung and colleagues focus on these mice in addition to mice deficient for the expression of the two major HIV coreceptors, CXCR4 and CCR5 (Maung et al., 2011). While the gp120 used in the transgenic construct utilizes CXCR4, which neurons are known to express, a critical role of CCR5 was found for gp120-induced neuropathogenesis. This supports the indirect toxicity of HIV on neurons and corroborates other studies linking HIV's neuropathogenic effects to chemokines and their receptors (Erichsen et al., 2003; Zhang et al., 2003; Kaul et al., 2007). Thus, this model provides an *in vivo* system for the further understanding of the CCR5-mediated pathway.

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A newer transgenic mouse model was developed to examine the effects of the HIV accessory protein Vpr, which was expressed in myeloid cells in the mice including in the CNS and peripheral nervous system (Jones et al., 2007; Acharjee et al., 2010). Power and colleagues review the studies on this model (Power et al., 2011). These mice manifest both structural and functional CNS abnormalities; in addition, they develop signs of peripheral neuropathy, which is quite prevalent in HIV-infected individuals. This peripheral neuropathy is linked, both in these studies in the transgenic mice and in humans, to effects on mitochondria. Interestingly, studies have examined the role of co-infection with hepatitis C virus (HCV), which is quite common in HIV-infected individuals including those with neuroAIDS. This was performed by direct CNS injection of HCV proteins in the transgenic mice, revealing addition neuronal damage. Thus, these studies exemplify how transgenic models can be used not only to isolate pathogenic factors but also to combine them and examine their effects and interaction *in vivo*.

A transgenic rat model has also provided insight into HIV neuropathogenesis. This model consists of rats transgenic for a *gag-pol*-deleted HIV-1 genome that is expressed in many tissues including the brain (Reid et al., 2001). Chang and Connaghan utilize this model to examine the interaction with drugs of abuse, specifically opiates (Chang and Connaghan, 2011). A wide range of interactions between the virus, the host response, and the morphine receptor and its ligands are described. Also, new data is presented in the HIV transgenic rats for the effects of the transgene in a preferred behavioral model for a drug of abuse (morphine). This remains of noted importance as substance abuse is among the most common co-morbid HIV conditions and affects treatment and outcomes (Altice et al., 2010). The bi-direction effects of drug abuse and HIV reflect the HIV pandemic in general and specifically in neuroAIDS.

The effects of viral proteins, injected directly into the brain, are also studied (Hayman et al., 1993). Yao and Buch explain distinct advantages to this system and provide examples of the range of studies possible (Yao and Buch, 2012). Using injection of the HIV protein Tat as the main model for the effects of HIV on the brain, they examined the effect of an additional injection of neuroprotective molecules and the use of transgenic models and chemical inhibitors for mechanistic studies. The use of mice in studies of monocyte migration into the brain, key in neuroAIDS, is also described, with examples including effects of the drug of abuse, cocaine.

To circumvent one of the major problems in studying HIV in small animals, the fact that HIV does not infect rodents, two additional rodent models using quite different technologies are also represented in this issue. Kelschenbach and colleagues focus on engineering the virus (Kelschenbach et al., 2011). By constructing a chimeric virus through the use of an envelope protein enabling the infection of mouse cells, *in vivo* infection can occur (Potash et al., 2005). They then use this model to examine the antiviral immune response. Through examining resistance to reinfection, both peripherally and in the brain, they show a role of CD8+ T cells in transferring immunity, indicating the potential utility of this model in studying host response and protective factors.

The final rodent model engineers the *in vivo* host itself. Gorantla and colleagues describe significant advancements in humanized mice (Gorantla et al., 2012b). While having a human immune system within an immunodeficient mouse host has allowed HIV infection in mice and the study of many virus/host cell interactions (Denton and Garcia, 2011), the ability to examine the effects of HIV on the brain had not been previously realized. Key findings, and the science behind them, are provided for the ability to include myeloid cells in HIV neuropathogenesis (Gorantla et al., 2010; Dash et al., 2011). Specific studies of HIV infected humanized mice brains are described, including non-invasive imaging studies to

examine not only structure effects of HIV on the brain but also key metabolic effects that can significantly impact neuronal and overall brain function (Gorantla et al., 2012a). Thus, in addition to the usual single time-point studies, longitudinal analyses for leukocyte migration and brain virus distribution can be studied (Gong et al., 2011), which in the current CART era of HIV infection are especially relevant.

A natural infection model is provided by feline immunodeficiency virus (FIV) infection, long recognized to be associated with neuropathogenesis (Dow et al., 1990). Similar to HIV, there is a relatively long asymptomatic period before the onset of disease, making it an attractive model for the effects of chronic infection. Meeker and colleagues show the use of this system in therapeutic development (Meeker et al., 2011). Using a synthetic ligand of a neurotrophin receptor, neuroprotection is demonstrated *in vitro* in a FIV/feline neural culture system. This can now be translated promptly into the *in vivo* system.

Three papers then cover the simian immunodeficiency virus (SIV)/non-human primate model. While natural infection of African monkeys by SIV is relatively nonpathogenic and provides important clues in the nature of disease induced by HIV, SIV infection of Asian monkeys (primarily rhesus and pigtailed macaques) is an important animal model for the effects of HIV *in vivo*, including the CNS consequences (Chahroudi et al., 2012). Given the similarities of SIV to HIV, and of monkeys to humans, many of the same molecules and functions can be assessed in monkeys using experimental protocols that cannot be done in humans.

Williams and Burdo utilized a rapid model of neuroAIDS in rhesus macaques, driven by depletion of CD8 cells via antibody treatment at the time of infection with SIV (Schmitz et al., 1999; Williams and Burdo, 2011). Since a high proportion of animals develop SIV encephalitis, this model can be used efficiently for CNS studies. Studies of monocyte/macrophage imaging, trafficking, turnover, and linked biomarkers of disease are described. As well as the application of experimental and therapeutic modalities are covered to understand key mechanisms of neuropathogenesis and its potential prevention and treatment.

Comorbid conditions affect many with HIV and neuroAIDS. Weed and colleagues investigated one aspect of the intriguing but often-conflicting reports on the effects of drugs of abuse on HIV pathogenesis through the use of cocaine treatment in SIV-infected pigtailed macaques (Weed et al., 2011). Two different doses of cocaine were studied in well-controlled experiments. Interestingly, although extensive studies were performed on virological, neuroinflammatory, and behavioral parameters, few differences were found in infected animals that could be attributed to cocaine administration. While the use of drugs of abuse is associated with risky behaviors including those leading to HIV infection, at least for cocaine under these conditions, no distinct effect of SIV on the brain was found.

The explosion of studies in the “omics” to capture complete datasets representing biological systems has included studies on animal models of neuroAIDS. Winkler and colleagues describe the studies done on characterizing the brain transcriptome in SIV infected rhesus monkeys at different stages of infection (Winkler et al., 2012). Through the use of bioinformatics, altered pathways were found at the different disease stages. In addition to studies on protein coding mRNA, regulatory microRNAs have also been examined in monkey brains. Given the similarities in SIV/HIV and monkeys/humans, both mRNA and microRNA studies were performed in monkeys and then directly compared to those performed in humans. A subset of both mRNAs and microRNAs were identified in common between studies of SIV and HIV encephalitis. Conveniently, open access information is given for the datasets from monkey and human studies, enabling future analyses including meta-analysis (Yelamanchili et al., 2010).

These papers represent an important collection of the current state of animal model work and point to future needs. In those with access to treatment, HIV infection has turned into a chronic disease. The ramifications of this change for neuroAIDS are still evolving, but it is clear that although the pattern of neurocognitive deficits as well as their severity may have changed, antiretroviral treatment has not reduced the prevalence of neurocognitive impairment in HIV infection (Heaton et al., 2011). As illustrated by the papers in this issue and others, animal models can be used not only to assess the effects of antiretrovirals but also adjunctive neuroprotective agents, enabling the testing of novel actions, pathways, and drug biodistribution as well as strategies to specifically deliver therapeutics to the brain (Eggert et al., 2010; Kanmogne et al., 2012).

Given their link to risk of infection and the prevalence of use in the infected population, the effects of drugs of abuse will continue to be a focus of investigation in clinical neuroAIDS (Byrd et al., 2011) and animal models of neuroAIDS, as indicated by several papers in this issue. While the advantage of controlling conditions in animal studies is huge compared to studies done in humans, investigators will continue to grapple with mimicking human patterns as well as the potential differences in the pharmacokinetics and pharmacodynamics of the drugs between humans and the animal species studied.

While animal studies are carried out under hypothesis driven experimental design, the insights that have been brought to light through unbiased profiling of “omic” investigations have been great in many fields including neuroAIDS. While transcriptomic work still dominates and will likely continue with the evolution from chip-based to high throughput sequencing technologies, contributions from proteomic and metabolomics studies should increase as these technologies further mature and become more accessible to investigators (Wikoff et al., 2008; Pendyala et al., 2010; Wiederin et al., 2010). Systems biology oriented analyses of such omic-based experiments will also drive new insights (Gersten et al., 2009).

Finally, with the now chronic nature of HIV, infected individuals can fortunately look forward to aging. How the other physiological changes associated with aging, as well as pathologies associated with aging, interact with those induced by HIV in this now chronic condition are not known. This is, of course, concerning for the brain, as the largest risk factor for neurodegenerative diseases is age. The effects of chronic HIV infection have some resemblance to accelerated aging, which has been linked to the presence of continued inflammation despite effective antiretroviral therapy (Deeks, 2011). The interplay between the immune and nervous system is clearly important in neuroAIDS, and the use of animal models to examine how chronicity and aging affect the changes HIV infection inflicts on the brain is an important current and future need (Kraft-Terry et al., 2009). In closing, we trust that the readership will find these articles illuminating not simply as a reflection of current research but of future trends in a cross disciplinary and highly evolving field.

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