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Transgenic Mice Expressing HIV-1 Envelope Protein gp120 in the Brain as an Animal Model in NeuroAIDS Research

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Abstract

HIV-1 infection causes injury to the central nervous system (CNS) and is often associated with neurocognitive disorders. One model for brain damage seen in AIDS patients is the transgenic (tg) mouse expressing a soluble envelope protein gp120 of HIV-1 LAV in the brain in astrocytes under the control of the promoter of glial fibrillary acidic protein. These GFAP-gp120tg mice manifest several key neuropathological features observed in AIDS brains, such as decreased synaptic and dendritic density, increased numbers of activated microglia and pronounced astrocytosis. Several recent studies show that brains of GFAP-gp120tg mice and neurocognitively impaired HIV patients share also a significant number of differentially regulated genes, activation of innate immunity and other cellular signaling pathways, disturbed neurogenesis, and learning deficits. These findings support the continued relevance of the GFAP-gp120tg mouse as a useful model to investigate neurodegenerative mechanisms and develop therapeutic strategies to mitigate the consequences associated with HIV infection of the CNS, neuroAIDS and HAND.

Keywords

HIV-1; gp120; NeuroAIDS; HAND; neuroprotection; transgenic animal model

Introduction

Infection with the human immunodeficiency virus-1 (HIV-1) and acquired immunodeficiency syndrome (AIDS) continue to present a major public health problem worldwide. Besides the progressive destruction of the immune system, HIV-1 causes a range of neurological problems and neurocognitive impairments that originally were described as

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Conflict of Interest Disclosure

The authors state that they have no conflict of interest.

NeuroAIDS but are now comprehensively categorized under the term HIV-associated neurocognitive disorders (HAND) (Antinori *et al*, 2007). While much information has been gained over the years regarding HIV-1 infection of the periphery and the central nervous system (CNS) in general, the pathological, cellular and molecular mechanisms leading to HAND, NeuroAIDS and AIDS remain incompletely understood. However, evidence has accumulated indicating that the CNS constitutes a HIV reservoir and thus also requires attention in all viral eradication attempts (Brew *et al*, 2015; Churchill and Nath, 2013; Ferretti *et al*, 2015; Gray *et al*, 2014; Joseph, 2015; Kramer-Hammerle *et al*, 2005; Lambotte *et al*, 2003; Nath, 2015).

Several lines of evidence stemming from the work of numerous investigators over many years strongly suggest that at least two major pathological mechanisms contribute to the development of NeuroAIDS, HIV-1 associated neurodegeneration and consequent HAND (reviewed in (Kaul, 2008)). The first is neurotoxicity caused by toxins released by infected or immune-stimulated, inflammatory microglia and macrophages (MΦ) in the brain, constituting an indirect injurious pathway, and/or direct damaging exposure to HIV-1 and its proteins (Giulian *et al*, 1990; Gonzalez-Scarano and Martin-Garcia, 2005; Kaul *et al*, 2001; Lindl *et al*, 2010). The second insult by HIV in the brain comprises the impairment of neurogenesis (Krathwohl and Kaiser, 2004; Okamoto *et al*, 2007; Poluektova *et al*, 2005; Tran *et al*, 2005).

Since HIV-1 was discovered and linked to the development of AIDS (Barre-Sinoussi *et al*, 1983; Hahn *et al*, 1984), multiple approaches have been taken to generate suitable animal models for studying HIV disease, including NeuroAIDS (Ambrose *et al*, 2007; Gardner and Luciw, 1989; Klotman and Notkins, 1996; Nath *et al*, 2000; Toggas and Mucke, 1996; Van Duyne *et al*, 2009).

Animal Models Utilized in AIDS and NeuroAIDS Research

The animal models for AIDS research include a range of species, such as chimpanzees and other non-human primates, cats and rodents (rats and mice) (Ambrose *et al*, 2007; Gardner and Luciw, 1989; Keppler *et al*, 2002; Klotman and Notkins, 1996; Nath *et al*, 2000; Reid *et al*, 2001; Toggas and Mucke, 1996; Van Duyne *et al*, 2009). Although chimpanzees can be infected with some HIV-1 strains, they rarely develop AIDS and were in the past primarily employed in vaccine research (Nath *et al*, 2000). However, chimpanzees in the wild can contract Simian Immunodeficiency virus (SIV) which appears to cause an AIDS-like disease (Keele *et al*, 2009). In any case, chimpanzees have apparently not been employed in studies of neuroAIDS. Other non-human primates, cats and rodents are resistant to productive HIV-1 infection, but several non-human primate species are susceptible to SIV and cats are permissive to a lentivirus called Feline Immunodeficiency virus (FIV) (Ambrose *et al*, 2007; Clements *et al*, 1994; Olmsted *et al*, 1989). Both SIV and FIV can dependably induce AIDS-like disease and neuropathological changes or even encephalitis in a species-specific manner, and macaques and cats have been used to investigate the pathogenesis of AIDS and NeuroAIDS (Ambrose *et al*, 2007; Clements *et al*, 1994; Clements *et al*, 2008; Jacobson *et al*, 1997; Meeker *et al*, 1997; Olmsted *et al*, 1989; Williams *et al*, 2008). SIV is considered to be the animal virus most closely related to HIV-1, but the existing significant differences

between the viruses have impeded the translation of findings into the human system, such as the development of vaccines. As an alternative approach to better adapt the SIV model for HIV research, several SIV-HIV hybrid viruses have been generated (Ambrose *et al*, 2007; Williams *et al*, 2008).

Rodents cannot be productively infected with wild-type HIV-1. However, two chimeric HIV mutants have recently been generated in which the viral envelope protein gp120 was replaced by the gp80 of ecotropic murine leukemia virus (EcoHIV) (Potash *et al*, 2005). This modification enabled for the first time a lasting lentiviral infection in mice that also triggered an immune response. Furthermore, one of the chimeric viruses was shown to be neuroinvasive, suggesting its potential suitability for NeuroAIDS research.

Certain immuno-compromised mouse strains can be reconstituted with a human hematopoietic system ('humanized mouse') which is permissive to HIV infection and thus enable small animal models for AIDS and NeuroAIDS research (Dash *et al*, 2011; Van Duyne *et al*, 2009). The intracranial injection of HIV-infected human monocyte-derived macrophages into the brains of mice with severe combined immunodeficiency (SCID) provides another model of NeuroAIDS and was used to demonstrate that HIV-infected macrophages can cause a neuropathology that shares key features with post mortem brains from HIV dementia patients (Limoges *et al*, 2000; Persidsky *et al*, 1996; Poluektova *et al*, 2002; Sas *et al*, 2007; Tyor *et al*, 1993). These studies also provided evidence that HIV-infection in the brain triggers a peripheral immune response.

Among the various model systems, rodents have turned out to be useful even though they cannot be productively infected with wild type HIV-1. However, one important advantage of rodents, both mice and rats, is that they can be genetically modified (Klotman and Notkins, 1996; Reid *et al*, 2001; Toggas and Mucke, 1996; Van Duyne *et al*, 2009).

Several transgenic mice and a rat have been generated that express an entire HIV genome and develop AIDS-like diseases (Hanna *et al*, 1998a; Hanna *et al*, 1998b; Iwakura *et al*, 1992; Leonard *et al*, 1988; Reid *et al*, 2001). The transgenic rat carries an HIV-1 provirus with functionally inactive *gag* and *pol* sequences which prevents the generation of infectious virus particles. However one HIV-transgenic mouse model and transgenic mouse microglia carrying the provirus of a macrophage-tropic HIV-1 were shown to release infectious virus (Leonard *et al*, 1988; Wang *et al*, 2003). Transgenic mouse models expressing the HIV genome in its entirety or distinct components of the virus, such as gp120, Tat or Vpr, in the brain develop various degrees of behavioral alterations as well as neuropathology, including loss of synapses, neuronal dendrites and neurons as well as glial activation, and thus recapitulate several pathological hallmarks of NeuroAIDS patients (Berrada *et al*, 1995; Bruce-Keller *et al*, 2008; D'hooge *et al*, 1999; Jones *et al*, 2007; Kim *et al*, 2003; Thomas *et al*, 1994; Toggas *et al*, 1994; Toneatto *et al*, 1999). Overall, the exact spectrum of pathological features with resemblance to AIDS and NeuroAIDS depends on the specific animal model and ranges from depletion of CD4+ T-cells to immunodeficiency to wasting disease to failure-to-thrive to neuronal injury and loss to behavioral impairment to shortened life span.

Of note, studies using HIV-infected humanized mice or transgenic expression of entire viral genomes or injection of HIV-infected macrophages in the brain are useful to investigate the combined pathological effects of all viral components, but cannot discern the potential contribution of a single viral factor. Therefore, approaches that use injection or transgenic expression of one viral component at a time appear very useful as well. The injection models have the advantage of deliberate and controlled timing of the application of any pathological agent into any experimental animal without requiring prior genetic modification. A limitation of many transgenic models, including the HIV-1 gp120tg mouse model that is the focus of additional sections of this article, is the constitutive expression of the transgene throughout the lifetime of the animals, which can in extreme cases prevent a normal or healthy development before onset of the desired pathological phenotype. One approach to avoid that potential caveat is the inducible expression of a transgene, such as the doxycycline-inducible HIV-1 Tat-tg mouse model (Fitting *et al*, 2010; Kim *et al*, 2003). However, doxycycline-inducible transgene expression requires continued exposure to the inducing compound and introduces an additional powerful agent into the experimental model that can have effects, at least temporarily, that are independent of the transgene expression. Moreover, expression-inducing agents could themselves modify the response of the model system to the induced transgene. Altogether, inducible and injection models seem most suitable to study acute or short–term effects of a pathological viral component. In contrast, transgenic models with constitutive expression may be more suitable to investigate long-term, chronic effects of viral proteins. On a separate note, transgenic models, such as the HIV-1 gp120tg mouse, that only express one viral protein, may miss pathological effects that originate from the combined action of different viral proteins. One approach to address this concern is the cross-breeding of transgenic models expressing different viral proteins.

Numerous studies have employed transgenic mouse models with both constitutive and inducible viral protein expression to address the pathological potential of HIV-1 components, such as gp120, Tat and Vpr, and indeed suggested that isolated viral factors can produce some of the pathological characteristics of HIV disease and NeuroAIDS (Bachis *et al*, 2006; Berrada *et al*, 1995; Bruce-Keller *et al*, 2008; Chatterjee *et al*, 2011; Hauser *et al*, 2009; Jones *et al*, 2007; Kim *et al*, 2003; Toggas *et al*, 1994; Toneatto *et al*, 1999). In comparison to all other animal models, mice have the additional advantage that many specific genetic knockout mutants are available. Thus, transgenic and genetic knockout mice permit studies of viral and host factors in ways that are not easily possible in other models. Therefore, it is perhaps not surprising that despite the above discussed limitations and disadvantages of constitutive transgenic expression, numerous studies have been performed with the first model that expresses HIV-1 gp120 specifically in the central nervous system.

HIV-1 gp120-Transgenic Mice as an Animal Model in NeuroAIDS Research

This article will focus on studies in the first reported HIV gp120-transgenic mouse model which expresses a soluble viral envelope gp120 of HIV-1 LAV in the brain in astrocytes under the control of the promoter of glial fibrillary acidic protein (GFAP-gp120-transgenic mouse/GFAP-gp120tg/HIVgp120tg) (Toggas *et al*, 1994). The transgene is expressed the highest in neocortex, olfactory bulb, hippocampus, tectum, selected white matter tracts, and along the glia limitans. Although this tg mouse only expresses viral gp120, it develops a

neuropathology that is strikingly similar to human AIDS brains, including decreased synaptic and dendritic density, frank neuronal loss, increased numbers of activated microglia and pronounced astrocytosis (Toggas *et al*, 1994) and thus a comparable neuropathology that results when HIV-infected human macrophages are intracerebrally administered into mice with severe combined immunodeficiency (SCID) mice (Persidsky *et al*, 1996; Tyor *et al*, 1993). The founder lines described in the first study of GFAP-gp120tg mice also suggested that neuropathology required a sufficiently high expression of gp120 RNA. Moreover, a peripheral immune challenge with recombinant gp160 triggered a strong lymphocyte-mediated immune response and infiltration of the brain only in gp120tg animals, but not non-tg littermate controls or in GFAP-LacZ tg mice, thus providing indirect evidence for the presence of viral envelope protein in the CNS of gp120tg mice (Toggas and Mucke, 1998). Several subsequent studies included an additional GFAP-gp120tg founder line that expresses more easily detectable envelope protein levels and therefore is called gp120tg *H*igh *P*rotein *E*xpressor, (HPX) line (Garden *et al*, 2002; Lee *et al*, 2011; Maung *et al*, 2014; Thaney *et al*, 2017; Toggas and Mucke, 1996). The studies discussed here served at least one of two purposes: either improving our understanding of the neuropathological mechanism(s) of HIV infection, or exploring potential future therapies for NeuroAIDS and HAND.

The Phenotype of GFAP-HIVgp120tg Mice

Histopathological studies of GFAP-gp120tg mice have so far primarily focused on cerebral cortex and hippocampus, because those brain structures are prominently affected in HIV patients with neurocognitive impairment (Toggas *et al*, 1994). Neuropathological features observed in GFAP-gp120tg mice include: 1) Loss of neuronal dendrites at 3, 4–5, 6, 10, 12 and 20 months of age (Garden *et al*, 2002; Kang *et al*, 2010; Maung *et al*, 2014; Thaney *et al*, 2017; Toggas *et al*, 1994)*(Maung and Kaul, unpublished)*, (see Figure 1 for immunofluorescence staining of cerebral cortex of 6 months-old mice); 2) loss of synapses at 3, 4–5 and 6 months (Maung *et al*, 2014; Thaney *et al*, 2017; Toggas *et al*, 1994); 3) activated microglia at 3, 4–5, 6, 10 months (Kang *et al*, 2010; Maung *et al*, 2014; Thaney *et al*, 2017; Toggas *et al*, 1994); 4) Astrocytosis at 3, 4–5, 6 and 10 months (Kang *et al*, 2010; Maung *et al*, 2014; Thaney *et al*, 2017; Toggas *et al*, 1994); 5) Compromised neurogenesis at 2, 4 to 5 and 8 months (Avraham *et al*, 2015; Avraham *et al*, 2014b; Crews *et al*, 2011; Fields *et al*, 2014; Lee *et al*, 2013; Lee *et al*, 2011; Okamoto *et al*, 2007; Steiner *et al*, 2015); 6) Behavioral impairment: GFAP-gp120tg mice display, in comparison to non-tg littermate controls, behavioral changes or impairment. At 6 months gp120tg mice show increased anxiety-like behavior in open field, light/dark transition task, and prepulse inhibition tests (Bachis *et al*, 2016). At 9 to 12 months, GFAP-gp120tg mice display reduced swimming velocity, and compromised spatial learning and retention (D'hooge *et al*, 1999; Hoefer *et al*, 2015; Maung *et al*, 2014) as well as reduced contextual but not cued fear conditioning *(Kaul et al., unpublished)*. GFAP-gp120tg mice also showed hyperactivity in an open field test compared to non-tg wild-type controls at 12 months of age (Fields *et al*, 2016a). 7) Alterations in electrophysiological function: In line with findings of behavioral changes or impairment and injury to neuronal presynaptic terminals and dendrites, electrophysiological studies detected abnormalities in short- and long-term potentiation in the CA1 region of the

hippocampus in gp120tg mice compared to non-tg controls at ~ 53 days and 10.5 months of age (Hoefer *et al*, 2015; Krucker *et al*, 1998).

Research Topics and Studies Using GFAP-HIVgp120tg Mice

1) Mechanism(s) of HIV-associated neurotoxicity and compromised neurogenesis

In comparison to non-tg controls, young but not 6 months-old GFAP-gp120tg mice presented with increased plasma corticosterone, and plasma and pituitary adreno-corticotropic hormone (ACTH) levels, indicating activation of the hypothalamic-pituitary axis (HPA) (Raber *et al*, 1996). The stimulation of the endocrine system depended on activation of *N*-methyl-*D*-asparate-type glutamate receptors (NMDAR), neuronal nitric oxide synthase (nNOS) and reactive oxygen species (ROS) as it was inhibited by the non-competitive NMDAR inhibitor memantine, the nNOS blocker N^G-methyl-*L*-arginine (LNMA) and a superoxide dismutase (SOD)-transgene (Raber *et al*, 1996). Hence, excitotoxic and oxidative stress appeared to be major contributors to HIVgp120-induced brain injury and possibly NeuroAIDS.

Along those lines, another study analyzed the brain's glutamate uptake systems, system XAG (sodium-dependent) and xc- (sodium-independent), in striatum and hippocampus. This investigation found (30–35 %) reductions in the kinetics of systems XAG and xc- in both neurons and glia of the striatum, but not hippocampus, of HIVgp120tg mice compared to non-tg wild-type controls (Melendez *et al*, 2016). Also, an increased number of spines in the amygdala and higher levels of brain-derived neurotrophic factor and tissue plasminogen activator were associated with an elevated level of anxiety-like behavior in 6 months-old GFAP-gp120tg mice in comparison to age-matched wild-type controls (Bachis *et al*, 2016). A proteomics study of synaptosomes found that the ratio of activated, phosphorylated to total Akt was diminished in forebrain of GFAP-gp120tg mice compared to non-tg wild-type controls, indicating compromised signaling of the pro-survival protein kinase pathway (Banerjee *et al*, 2012). This finding is in line with an earlier study showing that neuroprotection against neurotoxicity of HIVgp120 by physiological CCR5 ligands requires signaling of the Akt pathway (Kaul *et al*, 2007).

GFAP-gp120tg mice display clear signs of immune activation and neuroinflammation, including activated microglia and pronounced astrocytosis (Toggas *et al*, 1994). One early study reported increased amounts of the chemokines CXCL10 and CCL2 in brains of GFAP-gp120tg mice compared to non-tg controls (Asensio *et al*, 2001). The same study also observed an elevated number of $CD3^+$ T cells in GFAP-gp120tg brains.

Crosses of GFAP-gp120tg with CCR5KO mice led to several novel findings regarding the role of innate immunity in HIV-associated brain injury and behavioral impairment (Maung *et al*, 2014): 1) CCR5 was crucial *in vivo* for neuronal damage and behavioral impairment triggered by a CXCR4-using HIV/gp120; 2) CCR5 deficiency protected GFAP-gp120tg mice against impairment of spatial learning and memory; 3) Astrocytosis occurred independently of neuronal damage and behavioral impairment; 4) The acute phase protein lipocalin-2 (LCN2) was identified as a novel potential player in HIV-associated neuronal injury. Combining LCN2 with inhibition of CCR5 signaling provided a novel mechanism to

abrogate microglial activation and neurotoxicity of a CXCR4-using HIVgp120; 5) A genome-wide CNS gene expression analysis showed that brains of HIVgp120tg mice share a significant fraction of differential gene regulation with brains of HIV- and HIV encephalitis (HIVE) patients with neurocognitive impairment (Maung *et al*, 2014). The study revealed that GFAP-gp120tg brains mounted an immune response involving besides pro-inflammatory stimulation of macrophages, activation of nuclear factor κB (NFκB) by virus, Toll-like receptors (TLRs) and interferons (IFNβ and γ). The study might have translational implications by suggesting that HIV patients who are not elite controllers may benefit from pharmacological CCR5 inhibition even if they are infected with a CXCR4-preferring virus. The gene expression pattern indicative of a type I IFN signature was in accordance with an earlier report of IFN-stimulated gene (ISG)-15 in the brain of HIVgp120tg mice (Wang *et al*, 2012). A recent follow-up study confirmed that GFAP-gp120tg mice mounted a transient IFNβ response around 1.5 months of age (Thaney *et al*, 2017). While the mRNA expression for IFNβ had returned to baseline in 3 and 6 months-old animals, the signature of IFN-stimulated genes remained detectable.

Another earlier study suggested that activation of protein kinase C (PKC) may contribute to astrocytosis, a hallmark of neuroinflammation observed in HIVE and GFAP-gp120tg mice (Wyss-Coray *et al*, 1996). Similar to other neurodegenerative diseases, increased expression of matrix metalloproteinase (MMP)-2 has been associated with inflammation and neurodegeneration in brains of GFAP-gp120tg animals compared to non-tg littermate controls, (Marshall *et al*, 1998). Several studies found evidence of neuronal apoptosis in *post-mortem* brains of HIV patients with dementia (Adle-Biassette *et al*, 1995; Petito and Roberts, 1995; Shi *et al*, 1996). Introduction of a dominant negative interfering mutant of Caspase 1 (Casp1DN), an intracellular enzyme linked to regulation of apoptosis, into GFAP-gp120tg mice by cross-breeding protected neuronal dendrites, suggesting a critical role for the caspase system in HIV neurotoxicity (Garden *et al*, 2002).

The gp120 tg mouse model also presents with mitochondrial abnormalities like those observed in postmortem brain tissues from HIV-infected decedents (Fields *et al*, 2013; Fields *et al*, 2016b). Specifically, proteins controlling mitochondrial fission and fusion, dynamin-related protein (DRP) 1 and mitofusin (MFN) 1, respectively, are altered in brains of gp120 tg mice and in HAND decedents (Avdoshina *et al*, 2016; Fields *et al*, 2016b). In brains of humans and HIVgp120tg mice, decreased DRP1 and increased MFN1 are associated with enlarged and damaged mitochondria in neurons (Avdoshina *et al*, 2016; Fields *et al*, 2016b). Furthermore, in these translational studies, gp120 recombinant protein induced mitochondrial fusion through a reduction in DRP1 and an induction of MFN1 expression in neurons, in vitro (Avdoshina *et al*, 2016; Fields *et al*, 2016b). Potential therapeutic strategies to rectify these gp120-induced mitochondrial alterations will be discussed below.

To further investigate the roles of mitochondrial dysfunction, which leads to questions about altered autophagy, and persistent inflammation in the CNS, the GFAP-gp120tg mouse has proven an effective and relevant model that mirrors key features of the neuropathology observed in human NeuroAIDS. Original observations suggested that autophagy was increased in postmortem brain tissues of HIV patients (Zhou *et al*, 2011), however, later studies revealed autophagy markers are decreased in *post mortem* brain tissues of HIV

patients over the age of 50 (Fields *et al*, 2013). Remarkably similar to human brains, autophagy markers were also decreased in aged HIVgp120tg mice (Fields *et al*, 2013). Furthermore, decreased autophagy was associated with increased neuroinflammation and neurodegeneration. These effects were reversed by inducing autophagy function via gene delivery of beclin 1 (see below and (Fields *et al*, 2013)).

Since cART has transformed HIV infection into a chronic disease, evidence has emerged suggesting that long-term survival can be associated with an Alzheimer's Disease (AD)-like brain pathology (Brew *et al*, 2009; Green *et al*, 2005). Interestingly, normal human amyloid precursor protein expressed as transgene protected neurons of GFAP-gp120tg and control mice at ~ 5 months of age against acute or chronic excitotoxic injury (Masliah *et al*, 1997; Mucke *et al*, 1995). However, a triple transgenic mouse model expressing APP/PS1 mutants associated with AD and HIVgp120 displayed intraneuronal deposition of Aβ similar to brains of HIV patients (Bae *et al*, 2014; Green *et al*, 2005).

Accumulation of phosphorylated protein Tau (pTau) is another key feature of AD brains that was found in brain specimen of NeuroAIDS patients in comparison to age-matched healthy controls and GFAP-gp120tg mice, thus revealing another pathological feature of HIV-infected brains that is present in the tg mouse model (Kang *et al*, 2010). However, it remains to be elucidated if pTau is a contributing cause or mere consequence of HIVgp120-initiated CNS injury.

The GFAP-gp120tg mouse has been studied in another context related to cART. HIV-associated sensory neuropathy (HIV-SN) is a frequent neurological complication of the periphery in patients treated with dideoxynucleoside anti-retrovirals. GFAP-gp120tg mice exposed to didanosine (DDI) developed a distal degeneration of unmyelinated sensory axons, recapitulating the 'dying back' process associated with C-fiber loss seen in patients with HIV-SN (Keswani *et al*, 2006).

While HIV-1 seems unable to productively infect neurons, it has been reported that neural progenitor cells are permissive to the virus (Lawrence *et al*, 2004; Mattson *et al*, 2005; Schwartz and Major, 2006). However, independently of viral infection, HIV-1/gp120 was found to affect human and rodent neural progenitor cells (Krathwohl and Kaiser, 2004; Okamoto *et al*, 2007). Comparable to what has been observed in brain specimen from HIV dementia patients, the hippocampal dentate gyrus of GFAP-gp120tg mice presents with a reduction of proliferating neural progenitors in in comparison to non-transgenic controls (Okamoto *et al*, 2007). *In vitro* studies indicated that gp120 inhibited proliferation of neural progenitor cells via activation of a pathway comprising mitogen activated protein kinase p38 (p38MAPK), MAPK-activated protein kinase 2, a cell-cycle check-point kinase, and Cdc25B/C which in turn caused an arrest of the cell cycle in the G1 phase. Less neural progenitor proliferation in the presence of viral gp120 resulted in a smaller pool of progenitor cells to differentiate into neurons, thus impairing neurogenesis (Okamoto *et al*, 2007). Inhibition of hippocampal neurogenesis in GFAP-gp120tg mice was confirmed in subsequent studies, which implied roles for serotonin, cyclin-dependent kinase 5 (CDK5), fibroblast growth factor (FGF), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), cannabinoid $(CB)_2$ receptor, fatty acid amide hydrolase (FAAH), Cox2 and

prostaglandin E_2 (PGE_2) (Avraham *et al*, 2015; Avraham *et al*, 2014b; Fields *et al*, 2014; Lee *et al*, 2013; Steiner *et al*, 2015). One study found in brain specimen of HIVE patients and HIVgp120tg mouse brains evidence of aberrant activity of CDK5 and hyperphosphorylation of collapsin-response mediator protein-2 (CRMP2) which in turn can impair neurite outgrowth (Crews *et al*, 2011).

2) Effect of HIV in CNS on Behavioral Performance

GFAP-gp120-transgenic mice display in comparison to non-transgenic littermate controls an increased anxiety-like behavior at 6 months of age and additional behavioral changes or impairment at 9 to 12 months, such as altered escape latency, reduced swimming velocity, and impaired spatial learning and retention (Bachis *et al*, 2016; D'hooge *et al*, 1999; Hoefer *et al*, 2015; Maung *et al*, 2014; Patrick *et al*, 2011) as well as diminished contextual but not cued fear conditioning at 9 to 13 months *(Kaul et al., unpublished)*.

3) Interplay of HIV/NeuroAIDS and Drug Abuse

Abuse of drugs constitutes a major comorbidity of HIV infection and the associated neurocognitive impairment (Carey *et al*, 2006; Chang *et al*, 2014; Kapadia *et al*, 2005; Mitchell *et al*, 2006; Urbina and Jones, 2004) and the GFAP-gp120tg mouse model has been employed to investigate the combined effects of psychostimulant drugs and HIV-1 on the brain and behavior (Bandaru *et al*, 2011; Roberts *et al*, 2010; Soontornniyomkij *et al*, 2016).

GFAP-gp120tg mice showed in comparison to non-tg wild-type controls an altered acute response to Methamphetamine (METH) that was detectable as changes in stereotypic behavior (Roberts *et al*, 2010). In another study, transgenic gp120 expression in the brain was also associated with an increased preference for both METH and a highly palatable non-drug reinforcer (saccharin) as well as increased sensitivity to METH-induced conditioned reward (Kesby *et al*, 2012). These findings suggested an increased sensitivity to METH as a potentially underlying reason for a frequent abuse by HIV-infected individuals.

The potential additive or interactive effects of HIV proteins and drug abuse on neurocognitive deficits can be quantified using translational studies of mouse models such as the GFAP-gp120tg mouse. Such studies are more powerful with the implementation of behavioral paradigms that can be translated across species, e.g., to humans as well as rodents. In this manner, deficits that are observed in humans with HIV can also be examined in mice, contributing to the validity of the murine model and illuminating neurobiological substrates that are difficult to isolate in humans. One example of a cross-species paradigm is the behavioral pattern monitor (BPM), an extension of the traditional rodent open field that has been adapted for testing in humans (Perry *et al*, 2009; Young *et al*, 2016). Using the mouse BPM, one study assessed behavioral inhibition deficits in male and female mice, manifesting as increased motor activity, inappropriate perseverative behavior, and elevated exploratory response to novel stimuli (Henry *et al*, 2013). Female gp120tg mice who had been exposed to a chronic regimen of METH showed the highest level of exploration (hole-poking) compared to the other female mouse groups. The gp120tg mice exhibited less rearing and slightly less locomotion, relative to the wild-type mice. The findings suggested both gp120 expression and chronic METH exposure modified behavioral inhibition, but such

effects might be sex-dependent. Although robust gender differences have not been reported in human studies using the analogous behavioral paradigm (known as the human BPM), the findings in gp120tg mice underscored the importance of examining gender differences in HIV given potential gender or estrogen-related differences in HIV infection of the CNS (Wilson *et al*, 2006).

A further example of translation between species can be illustrated with the prepulse inhibition (PPI) paradigm. PPI is a measure of sensorimotor gating and is regulated by a network of neural structures including the dopaminergic circuitry implicated in inhibitory function. PPI can be assessed across species. Impaired sensorimotor inhibition, measured by PPI of the eyeblink startle response, was observed in HIV-infected persons with neurocognitive impairment compared to cognitively intact HIV-infected persons (Minassian *et al*, 2013), suggesting that early inhibition deficits accompany or may even precede downstream cognitive impairment in HIV-infected individuals. In rodents, PPI is quantified using the whole-body startle response, and PPI in GFAP-gp120tg and METH-exposed mice was studied (Henry *et al*, 2014). Prior to chronic METH exposure, female gp120tg mice exhibited decreased PPI compared with female wild-type mice, whereas male gp120tg mice showed increased acoustic startle response compared with the other groups. These findings in rodents, along with the results in humans indicating PPI deficits in HIV-infected persons with neurocognitive impairment (Minassian *et al*, 2013), suggest that inhibition deficits, which likely reflect HIV- and METH-related alterations in dopaminergic signaling, may not occur as a global phenomenon but may emerge in association with higher-order cognitive deficits or biological variations, e.g., those affected by sex.

In another study, GFAP-gp120tg mice were exposed to an escalating-dose, multiple-binge METH regimen at 3–4 months of age (Hoefer *et al*, 2015). Potential long-term effects were investigated after 6–7 months of drug abstinence employing behavioral tests and analyzing neuropathology, electrophysiology and gene expression. Behavioral assessment revealed impaired learning and memory in both gp120tg and wild-type animals treated with METH. Neuropathological analysis showed that METH triggered similarly to HIVgp120 a significant loss of pre-synaptic terminals and neuronal dendrites in hippocampus and cerebral cortex of wild-type animals. Electrophysiology experiments with hippocampal slices revealed that METH exposed GFAP-gp120tg animals displayed reduced post-tetanic potentiation, whereas both METH and gp120 expression led to reduced long-term potentiation. Arrays of quantitative reverse transcription-polymerase chain reaction exposed a significant dysregulation of specific components of GABAergic and glutamatergic neurotransmission systems in response to gp120 expression, METH and their combination, providing a potential mechanism for synaptic dysfunction and behavioral impairment. Thus, both HIVgp120 and METH caused lasting behavioral impairment in association with altered gene expression and neuropathology. However, the combination of METH exposure and HIVgp120 expression produced the most pronounced, long lasting pre- and post-synaptic alterations in conjunction with impaired learning and memory (Hoefer *et al*, 2015). The same conclusion regarding learning and memory was drawn in a separate behavioral study using the same METH regimen in GFAP-gp120tg mice (Kesby *et al*, 2015b). A cross-species study investigated in both humans and GFAP-gp120tg mice the separate and combined effects of METH and HIVgp120 on learning and executive functions (Kesby *et al*,

2015a). The results demonstrated that HIV in humans and viral gp120 in mice each impaired learning. Furthermore, a history of METH exposure appeared to aggravate HIV-associated neurocognitive deficits in both species. Overall, the similar pattern of outcomes in both species suggested that the viral envelope protein gp120 could significantly contribute to learning deficits in HIV patients.

Morphine exposure was found to increase oxidative stress and post-synaptic damage in brains of GFAP-gp120tg and non-tg control mice (Bandaru *et al*, 2011). Upon withdrawal the altered response to oxidative stress and synaptic damage was largely reversed in non-tg but not gp120tg brain. Moreover, GFAP-gp120tg brains displayed compared to non-tg controls an altered Sphingomyelin metabolism with elevated levels of ceramide. Ceramide has been implicated in neuronal injury and cell death pathways and although morphine reduced ceramide levels, withdrawal restored the elevated concentrations in GFAP-gp120tg mice (Bandaru *et al*, 2011).

4) Exploration of treatments or prevention of HIV-associated brain injury

Numerous studies have employed the GFAP-gp120tg mouse model to explore potential therapeutic strategies for HIV-induced brain injury and the associated neurocognitive disorders. Since it was recognized that HIV damages the brain not only through neurotoxicity but also by compromising neurogenesis and thus affects basic homeostasis and repair, the studies have targeted both pathological mechanisms (Kaul, 2008; Krathwohl and Kaiser, 2004; Okamoto *et al*, 2007). Several studies found evidence that regulation or inhibition of CDK5 using pharmacological or genetic approaches or exercise rescued hippocampal neurogenesis in GFAP-gp120tg mice. The successful approaches included CDK5 knockout, the cell cycle inhibitor roscovitine, the tyrosine kinase inhibitor sunitinib and an exercise-induced increase of BDNF expression (Fields *et al*, 2014; Lee *et al*, 2013; Patrick *et al*, 2011; Wrasidlo *et al*, 2014). However, exercise and selective serotonin re-uptake inhibitors (SSRI) also restored hippocampal neurogenesis in GFAP-gp120tg mice (Lee *et al*, 2011; Steiner *et al*, 2015). The exact mechanism(s) remain to be elucidated but appear to involve reduced susceptibility to excitotoxic injury. The genetic knockout of FAAH which results in increased expression of Cox2 and production of PGE2 and activation of the CB_2 receptor were also found to enhance neurogenesis in GFAP-gp120tg mice while concomitantly diminishing astrogliosis (Avraham *et al*, 2014a; Avraham *et al*, 2015). These two studies suggested that a reduction or modulation of initially pro-inflammatory pathways promoted neurogenesis specifically in GFAP-gp120tg/FAAH-KO mice since, in contrast, non-tg FAAH-KO animals showed impaired neurogenesis (Avraham *et al*, 2015).

An early study aiming to protect the brain and specifically neurons from HIV-1 induced excitotoxic injury treated GFAP-gp120tg mice with the non-competitive NMDAR inhibitor memantine (Toggas *et al*, 1996). Memantine applied over a six-week period prevented damage to neuronal dendrites and presynaptic terminals in the mouse model. A subsequent clinical study of the NMDAR antagonist suggested an improvement of the pathologically disturbed neuronal metabolism but produced no significant improvement of neurocognitive performance in impaired HIV patients (Schifitto *et al*, 2007). A more recent study used a modified version of memantine, called nitro-memantine, as a pharmacological tool in

comparison with genetic manipulation of NMDAR activity through overexpression of the modulatory subunit GluN3A in the GFAP-gp120tg mouse (Nakanishi *et al*, 2016). Although both nitro-memantine and GluN3A inhibited NMDAR activity, only nitro-memantine protected pre-synaptic terminals in HIVgp120tg mice, whereas overexpression of GluN3A caused itself significant neuronal damage. It was hypothesized that nitro-memantine predominantly interacted with pathologically activated extrasynaptic activated NMDARs, whereas GluN3A overexpression may have disturbed normal activity of synaptic and extrasynaptic NMDARs (Okamoto *et al*, 2009).

As mentioned above, the brains of both humans with HAND/dementia and GFAP-gp120tg mice present with hyperphosphorylated tau protein, which has been implicated in neuronal damage and loss. Intranasal treatment of 6 months-old GFAP-gp120tg for 4 months with a combination of erythropoietin and insulin-like growth factor I (EPO+IGF-I) provided neuroprotection in association with increased phosphorylation/activation of Akt (PKB) and phosphorylation/inhibition of glycogen synthase kinase (GSK)-3β, which notably reduced downstream hyperphosphorylation of tau (Kang *et al*, 2010).

The GFAP-gp120tg mouse provides a relevant model to test therapeutic strategies targeting dysfunctional autophagy and mitochondrial function in the brain. As proof of concept, gene delivery to the brains of aged gp120tg mice of Beclin 1, a key protein for the initiation of autophagy, restored levels of autophagosomes and reduced neurodegeneration and neuroinflammation (Fields *et al*, 2013). The beneficial effects of increased autophagy may result from increased clearance of protein aggregates and/or through recycling of damaged mitochondria via mitophagy. Further evidence for the neuroprotective effect of increasing the recycling of damaged mitochondria was illustrated in subsequent studies in which DRP1 gene delivery promoted mitochondrial fission, a prerequisite for mitophagy, and reduced neurodegeneration (Fields *et al*, 2016b).

A more recent study using the gp120 tg mouse suggests that anti-inflammatory molecules may also provide protection from gp120-induced neurotoxicity (Fields *et al*, 2016a). The immunosuppressive compound FK506 reduced neuroinflammation and neurodegeneration in the gp120 tg mouse model. FK506 also partially restored mitochondrial abnormalities in the gp120 tg mice, however, treatment did not restore DRP1 levels to those of control mice (Fields *et al*, 2016a). These data suggest that reducing neuroinflammation is a promising therapeutic strategy for HAND, though, more mechanism-directed approaches, such as targeting autophagy or mitochondrial dynamics, may prevent the initiation of neuroinflammation.

HIV-1 infection triggers an innate immune response including type I interferons (IFNα and β)(Doyle *et al*, 2015; Poli *et al*, 1994; Xiang *et al*, 2004). However, chronic expression of IFNα in the HIV-1 infected CNS has been linked to cognitive impairment and inflammatory neuropathology (Sas *et al*, 2009; Sas *et al*, 2007). In contrast, IFNβ has been implicated in the control of HIV and SIV infection in the brain (Barber *et al*, 2004; Kitai *et al*, 2000). A recent study showed that IFNβ confers neuronal protection against HIVgp120 toxicity and GFAP-gp120tg mice mount a transient IFNβ response with IFNβ mRNA significantly increased in brains at 1.5, but not 3 or 6 months of age (Thaney *et al*, 2017). Neuroprotection

by IFNβ against toxicity of HIVgp120 required IFNα receptor 1 (IFNAR1) and the β-chemokine CCL4. Moreover, a four-week intranasal IFNβ treatment of HIVgp120tg mice starting at 3.5 months of age increased expression of CCL4 and concomitantly abrogated gp120-induced damage to neuronal dendrites and pre-synaptic terminals in hippocampus and cerebral cortex (Thaney *et al*, 2017). Altogether, the results suggested exogenous IFNβ as a neuroprotective factor that has potential to ameliorate *in vivo* HIV-induced brain injury.

Future Studies Utilizing the HIVgp120tg Mouse Model

The body of published studies that used the GFAP-gp120tg mouse model suggests its suitability for investigating several open questions in neuroAIDS research, including: 1) The role of host factors in HIV-associated brain injury; 2) Eradication of viral sequences – the transgenic HIV gp120 constitutes an original viral sequence integrated in the host genome. Although the viral sequence is expressed only in the CNS, the integrated DNA sequence is present in the genome of all tissues; 3) Investigation of effects of abused drugs and cART on HIV-associated brain injury, behavior and neural circuitries. The published studies on the effects of METH and morphine in GFAP-gp120tg mice strongly suggest that this mouse model will be useful to investigate the impact of other drugs as well, such as nicotine, cannabis, cocaine and prescription painkillers; 4) The effect of Aging on HIV-associated brain injury – GFAP-gp120tg mice can be aged to reach 20+ months of age (Maung *et al*, 2014); and 5) The continuing exploration of strategies for treatment or prevention of HIV-associated brain injury, and behavioral impairment that characterizes HAND. All current animal models have limitations, but an in-depth analysis of existing models for HIV disease of the CNS, such as the GFAP-gp120tg mouse discussed here, and their utilization for pre-clinical intervention studies still has potential to provide invaluable information.

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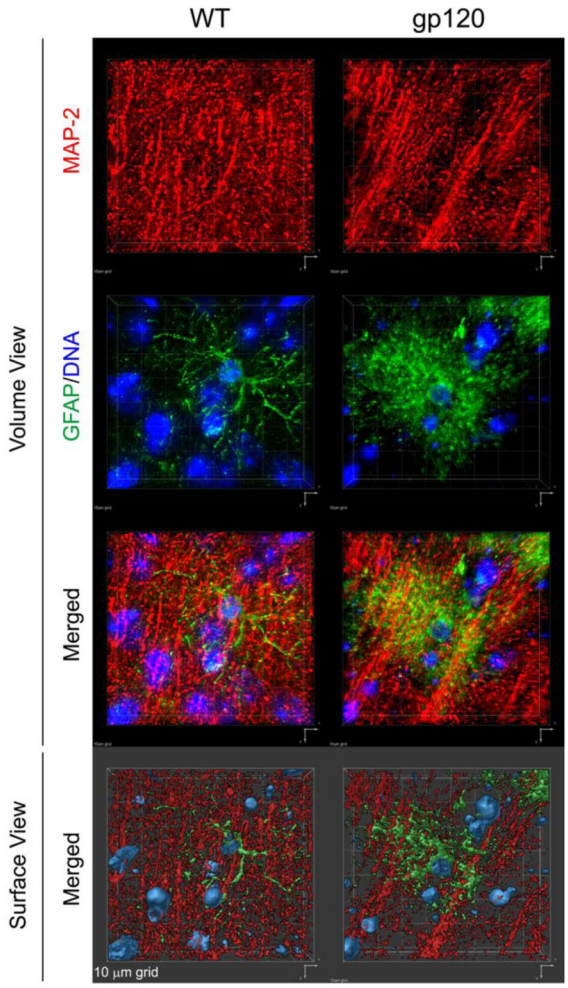

Fig. 1. Immunofluorescence staining of MAP-2-positive neuronal dendrites and GFAP-positive astrocytes in cerebral cortex of HIV gp120-transgenic and non-transgenic, wild type control mice

Sagittal brain sections of 6 months-old gp120-transgenic and wild-type (WT) littermate controls were immune-stained for neuronal MAP-2 (red) and astrocytic GFAP (green). DNA (blue) was labeled with H33342 and is shown to indicate nuclei. Fluorescence-labeled sections were analyzed using a Zeiss Axiovert 100 M inverted microscope and Slidebook software (Intelligent Imaging Innovations, Denver, CO) to record Z-stacks and perform deconvolution and 3D reconstruction. The upper six panels show 3D volume views, the bottom two panel are 3D surface views. Representative areas of mid-frontal cortex, layer 3, are shown. Note the difference in the density of MAP-2 immunoreactive neuropil and astrocyte morphology between WT and gp120tg samples, and the dimensions of the 10 μm grid.