PROJECT SUMMARY (See instructions):

Abstract

The pace of scientific discovery is often dictated by the development of new tools and techniques that bring into focus previously imperceptible aspects of biology and anatomy. In neuroscience, the development of new labeling methods, such as the Golgi stain in the 1870s or heterologous expression of fluorescent proteins in the 1990's, continues to revolutionize our ability to dissect brain circuits and study how they function to support behavior, learning and memory.

Today, the heterologous expression of genes, like those encoding fluorescent proteins, calcium sensors, and light-gated channels dominates the research landscape. The desire to easily express foreign genes with increasing precision has made viruses indispensable tools in many neuroscience laboratories. In mouse research, viral vectors are often used in conjunction with cell type specific Cre recombinase transgenic lines to target distinct neuronal populations. In the many other laboratories using non-transgenic animal models, such as primates, rats, chickens and songbirds, viruses serve as the simplest method for heterologous gene expression of fluorescent proteins and other molecular tools. Although these methods have proven to be powerful, currently available replication competent viruses and non-replicating viral vectors suffer from several limitations, including low infection rates, regional specificity, variable expression, toxicity, and small packaging capacities. The goal of this research is to identify a new suite of viruses that outperform these current standards.

Pairing the expertise of virologists (Schoggins laboratory) and system neuroscientists (Roberts and Xu laboratories) our research team will systematically test the utility of several viral platforms that are relatively understudied in brain research. We have identified 20 viruses representing 7 families and 12 genera that may have the potential for use in neuroscience research. We will test the ability of these viruses to drive expression of green fluorescent protein (GFP) in mice and birds**.** In the first phase, we will test replication and expression of all viruses following targeted intracranial injections in mice and songbirds. In the second phase, we will focus on viruses seen to effectively infect neurons and quantitatively examine infection rates, regional specificity of infections, timeframe of infections and viral toxicity. In the third phase, focusing only on best candidate viruses as determined in phases I & II, we will design replication incompetent viral vectors and test the utility of these constructs for the robust and stable expression of molecular tools in vivo.

This innovative approach has the strong potential to identify one or more new viral vectors that express unique characteristics, such as high and stable infection rates, larger packaging capacities and unique patterns of transsynaptic or cell contact based labeling within the central nervous system. By partnering virologists and neuroscientists, this research can identify the next generation of viral vectors for neuroscience and broadly impact the way researchers express molecular tools in the brain.

RELEVANCE (See instructions):

Viruses have evolved over millions of years to evade detection and thrive in vertebrate hosts. Building on the evolutionary diversity of vertebrate viruses, we will examine the use of several, previously untested, viral species for neuroscience research. This innovative project is relevant to the intent of the UT BRAIN seed grant because it establishes a new and unique research partnership between virologists and neuroscientists, between the departments of Microbiology and Neuroscience, and between the graduate programs of immunology, molecular biology and neuroscience at UT Southwestern. In addition, we propose to identify, and apply new viral vectors for labeling and expressing molecular tools in large populations of neurons, a goal that is central to the goals of the federal BRAIN Initiative. Therefore, this research is likely to yield future funding from NIH. During the execution of this project the Schoggins laboratory will produce and maintain all viral strains. The Xu and Roberts laboratories will conduct all experiments in mice and songbirds, respectively. The three labs will work together closely in order to rapidly identify the next generation of viral vectors that can be of use to the broader neuroscience community.