Grant Training Center

1901 N Fort Myer Drive
Suite 1016
Arlington, VA 22209

NIH Statement of Significance Examples

Statement of Significance Example #1

Proposal Title: Structure and Function of Flaviviruses

The amount of structural information on flaviviruses has greatly increased during the last five years [**47**], the period of our previous Program Project Grant (1 P01 AI055672). During this time, using a combination of crystallography and cryoEM, we have determined the structure of the immature [**3, 4**] and mature [**12, 27, 28**] dengue and West Nile viruses, the post-fusion structure of the external glycoprotein has been determined [18, 19] and complexes of flaviviruses with receptor [**6**] and neutralizing antibodies [**48**] have been the subject of structural studies. These results show that there are enormous conformational changes that occur during virus maturation, host cell recognition and fusion with the host cell. These dynamic events are at the center of the virus life cycle and would be the target of many antiviral strategies. However, there is currently little or no information on the mechanisms that guide and direct these enormous structural transitions. The various specific aims of this grant application are directed to intercept the virus in its assembly and infection processes. We have started to use antibodies, pH adjustments, and rapid freezing techniques to study the various intermediates, as well as improving the resolution of all present and future structural investigations. These studies are also starting to provide information on the various mechanisms by which antibodies neutralize flaviviruses.

It has been our universal experience that inspection of structure, when newly available, is a wonderful stimulus to answer questions about how the structure functions to perform its multiple tasks. The various structures of flaviviruses and their assembly and functional intermediates that we anticipate will become available during the tenure of this grant is likely to lead to fuller analyses of the viral assembly pathway, the initial virus-cell recognition event, and the endocytotic processes that lead to fusion with the cell membrane. In addition, we anticipate that the knowledge we will gain by the study of flaviviruses will be applicable to many other viral systems.

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Statement of Significance Example #2

Proposal Title: Resistance Suppression for Influenza Virus with Combination Chemotherapy

Mathematical modeling of pandemic influenza suggest that such a pandemic could be controlled with the judicious use of antiviral drugs, wide spread vaccination against pandemic influenza strains, and non-pharmaceutical measures such as school closing and working from home, etc (70-75). Thus, with the appropriate use of nonpharmaceutical interventions and antiviral drugs in the short term and vaccination in the long term, it should be possible to contain epidemics and pandemics caused by avian or human influenza viruses. Now the questions that remain are: how much drug to give and how often does one have to give that much drug to prevent infection or cure a patient infected with epidemic or pandemic strains of influenza virus without allowing resistant viruses to emerge during therapy? We **hypothesize** that there is an optimal dose of each of these influenza virus drugs or combinations of drugs and an optimal schedule of administration of these drugs and combinations of drugs that will prevent and/or cure infection with avian or human influenza viruses without leading to the emergence of drug resistant viruses during therapy.

Since it will not be possible to determine the effect of these antiviral compounds on H5N1 or other epidemic and pandemic influenza virus infections in people in the standard phase II – III clinical trials, we shall use our *in vitro* HFIM system, developed by Dr. Drusano, the PI of this grant application (7- 16), to determine the optimal dose and administration schedule for amantadine (for type A viruses) and oseltamivir carboxylate for type A and type B viruses. Several H1N1 and H3N2 human influenza A viruses, the recombinant virus, rgA/Vietnam/1203/2004 X A/PR/8/34, (a surrogate for H5N1 influenza virus), and type B viruses will be tested. Once we have determined the pharmacodynamically-linked variable for each of these antiviral compounds given as monotherapy for these viruses, we will determine the effects of combinations of these compounds on virus replication in the HFIM system. Since it is known that treatment of influenza virus-infected individuals with the amantadine or oseltamivir carboxylate can lead to the emergence of drug resistant viruses during therapy (1-6), a major aim of this proposal will be to determine the dose and schedule of administration of these drugs that will suppress the emergence of resistant viruses when these drugs are delivered as monotherapy or in combination therapy.

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Statement of Significance Example #3

Proposal Title: Effects of Attention Disorders on Developing Cognition: Mechanisms and Plasticity

A fundamental question about human cognition is the extent to which it is predetermined to take its adult shape, or is instead malleable and dependent on learning from the environment. This question naturally brings researchers to investigate the early development of cognitive functions, and theoretical positions have coalesced around distinct alternatives. Nativists propose that infants come to the world equipped with a sophisticated armament of skills and conceptual knowledge. Claims of innate specification of cognitive domains have been bolstered by dissociations of function in individuals with developmental disorders, especially those associated with a known genetic aetiology. Constructivist accounts instead see environmental input as instrumental and question the notion of developmental disorders as islets of intact and impaired ability.

A way to turn impasse into dialogue is to ask how domain-specific knowledge emerges through domaingeneral processes such as attentional control: active selection of information in the environment gates processing into short-term and long-term memory. Executive processes also provide the mental workspace necessary to select or ignore, update and maintain information online and therefore constrain domainspecific learning both concurrently and longitudinally. Attention and executive deficits could lead to cascading effects across many domains of cognition, with uneven cognitive profiles resulting from interactions between attentional biases and characteristics of the to-be-learned information. In this context, studying individuals with disorders of attention and executive control from early childhood, rather than just in adulthood, has the potential to assess disorders' role in substantiating the innate specification and modular structure of cognition.

Work in my laboratory has investigated disorder-specific profiles of early attention difficulties in developmental disorders that are either genetically or functionally defined, as well as their trajectories and outcomes on behaviour and cognition. Understanding how distinct attention disorders affect cognitive processes has required a prospective longitudinal approach and experimental paradigms that can tap attention and executive control in young and less able children. In a complementary fashion, we study optimal interactions of attention and executive control with memory and learning over typical development, from early childhood into adulthood.

The data emerging from these studies at the interface between attention disorders and their cascading effects on cognition have generated novel questions. How do deficits influence interactions with naturalistic environments? Are attention deficits predetermined to follow their course, or instead malleable? I propose to study how attention and executive control mediate outcomes across cognitive domains and in everyday situations such as complex classroom environments. Importantly, in order to test the plasticity of attention difficulties and their effects on other cognitive processes, I propose to contrast controlled training regimes that

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modify domain-general mechanisms like attention (training children in "how to learn") with domainspecific interventions (training them on "what to learn"). These two complementary approaches will target core questions about mechanisms fostering the developing mind, because they will test the efficacy and specificity of attention training effects across cognitive domains, and the extent to which attention deficits associated with an identified genetic aetiology or high familial risk are amenable to environmental influences.