Disease Models & Mechanisms 3, 263-264 (2010)

DMM Travelling Fellowship awards

Scientific discovery is facilitated when creative minds and unique perspectives come together. Therefore, Disease Models & Mechanisms (DMM) enables collaborations between clinical and basic science researchers who work with model organisms to understand or treat human disease. DMM Travelling Fellowships encourage graduate students or postdocs to combine the expertise of their immediate colleagues with the technical or conceptual advancements of scientists outside their laboratories. These awards offer up to £2500 (or currency equivalent) for collaborative visits to other laboratories. This money is intended to offset the expenses incurred through travel, or other expenses related to initiating a new collaboration outside the host lab institution.

Here are a few of the exciting projects that have recently received support from DMM:

Mice with autoimmune encephalomyelitis provide insight into multiple sclerosis

Multiple sclerosis (MS) is a devastating chronic neurological disease, which affects approximately 2 million people worldwide. In this autoimmune inflammatory disorder, the T-cell response creates much of the characteristic inflammation and disease-associated pathology. MS patients have characteristic areas of demyelination within the central nervous system (CNS) that inhibit communication along the axons of neurons in the brain or spinal cord. The key event in MS development is thought to be the breakdown of immune tolerance to CNS self-antigens in genetically susceptible individuals, which leads to myelin sheath breakdown.

Experimental autoimmune encephalomyelitis (EAE) is an inflammatory disease of the CNS. EAE shares many similarities with MS and it is studied in mice as a model for human MS. This model experiences clinical symptoms (spontaneous relapses and remissions) and histological manifestations, which closely parallel the course of MS in human patients. This model provides meaningful insight into the role of inflammatory mediating cytokines, such as interferon gamma (IFN-γ), in the disease process. IFN-γ is an important regulator of T-cell activation, but the role of IFN-γ in the pathogenesis of CNS inflammation is still very cryptic. Conflicting data, suggesting that IFN-γ can contribute to inflammation in disease or serve in a protective capacity, leads to confusion in this area of research.

Ruth Benson from the University of Manchester in the UK works with a mouse model that allows for tissue-specific modulation of IFN-γ receptor 2 (IFNγR2) expression. She is collaborating with Dr Becher's laboratory from the University Hospital of Zurich in Switzerland, which has expertise in autoimmunity and the role of inflammation in diseases of the CNS. Using mouse models they aim to define the role of IFN-γ in the inflammation-induced pathology that characterizes MS.

Modulating behavior associated with fragile X syndrome in a zebrafish model

Fragile X syndrome (FXS), an X-linked dominant disorder with reduced penetrance, is the most common form of inherited mental retardation. Its incidence is estimated at 1 in 4000 males and 1 in 8000 females. FXS patients experience a range of mental disabilities that are associated with a lack of the fragile X mental retardation (FMRP) protein. The primary phenotype of FXS at the cellular level is elongated and immature dendritic spines in neurons of the CNS. The cognitive phenotype probably demonstrates a need for FMRP in both the maturation of neuronal circuits and in maintaining the synaptic plasticity of the adult brain, which allow for the ongoing refinement of neural circuits.

The zebrafish model provides a tractable system to study early neuronal development. Since it is possible to genetically manipulate zebrafish using morpholino antisense technology, it is possible to examine the genetics of neuronal disease. The zebrafish embryos are transparent and it is possible to administer various pharmacological compounds to the embryos. Zebrafish are amenable to in vivo imaging of early neuronal development and the effects of neurological phenotypes can be connected with their corresponding behavioral phenotypes.

Justin Cowan at the University of Oxford in the UK is collaborating with Dr Concha at the University of Chile to develop systems for evaluating treatments that target post-translational mechanisms of neuronal development. They are evaluating the influence of modulators on the neuronal morphologies and the behavioral phenotypes of a zebrafish model of FXS. These efforts aim to develop meaningful behavioral phenotyping assays of this zebrafish model. Using time-lapse in vivo confocal microscopy, they are characterizing the effect of potential pharmacological treatments on neuronal morphology.

Generating new motor neurons after spinal cord injury in zebrafish

Spinal cord injury and degenerative diseases caused by a loss of motor neurons often lead to irreversible damage and permanent disability. Treatments for spinal cord injury patients are limited significantly by the inability of motor neurons to regenerate. Stem cells offer hope to improve our understanding of these diseases and to develop potential cures.

The genes involved in motor neuron differentiation are highly conserved between zebrafish and humans. Thus, studying the functions of molecules in zebrafish is greatly predictive of the situation in mammalian systems that are often more complicated and difficult to study. Screens of zebrafish embryos revealed a number of small molecules expressed in the descending neurons

that innervate the spinal cord. These molecules influence the differentiation of motor neurons and it is thought that these molecules might be manipulated in cells in order to induce new motor neurons after spinal cord injury.

Anton Barreiro-Iglesias at the University of Santiago de Compostela in Galicia in Spain is investigating the role of the Robo/Slit axonal guidance system in the regeneration of descending axons. He is collaborating with Dr Becker's lab at the Centre for Neuroregeneration in Scotland, which has extensive experience of using zebrafish as a model for spinal cord injury. They hope that, by expressing differentiation molecules in zebrafish neurons, they will be able to restore motor function in injured fish.

Gene therapy for patients with severe combined immunodeficiency

Genetic defects in the adenosine deaminase (*ADA*) gene are among the most common causes for severe combined immunodeficiency (SCID). ADA-SCID patients suffer from lymphopenia; a lack of cellular and humoral immunity; failure to thrive; recurrent infections; and a battery of additional autoimmune problems. Currently available therapeutic options for this otherwise fatal disorder are relatively invasive and labor intensive, including bone marrow transplantation, enzyme replacement therapy or hematopoietic stem cell gene therapy. Although varying degrees of immune reconstitution can be achieved by these treatments, other autoimmune manifestations, including type I diabetes, hypothyroidism, autoimmune thrombocytopenia and hemolytic anemia, still frequently plague these patients.

In normal individuals, self-reactive antibodies are removed at different checkpoints of B-cell development in the bone marrow and peripheral blood. The increased formation of autoantibodies in SCID patients may result from inefficient checkpoint regulation during the development of ADA-deficient B cells.

Aisha Sauer from San Raffaele University in Italy is collaborating with Dr Meffre's lab at Yale University in the USA to define the mechanisms that are responsible for the pathophysiology of ADA deficiency, with the hope of improving current treatment options for ADA-SCID patients.

Dopamine receptor sensitivity in a model of Parkinson's disease

Parkinson's disease (PD) is a movement disorder that involves progressive degeneration of the CNS. It is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, which is an area of the brain that controls motor coordination. This is followed by dopamine (DA) depletion in the neostriatum, an area in the forebrain that regulates input signals.

A widely employed experimental model of PD uses the neurodegenerative toxin, 6-hydroxydopamine, to unilaterally destroy dopaminergic neurons. In this model, striatal DA depletion is followed by dopamine D3 receptor (D3R) supersensitivity. D3R is implicated in the pathogenesis of PD, but its role is currently unknown. Supersensitization of the receptor involves signaling changes and an altered pattern of D3R surface expression. D3R activity is closely regulated in cells and can be modulated by its interactions with soluble molecules and other neurotransmitter receptors.

Aleph Prieto from the National Autonomous University of Mexico is collaborating with Dr Franco's laboratory at the University of Barcelona in Spain to determine the effect of DA depletion on D3R and the ability of the receptor to interact with other G protein-coupled receptors. They are using a variety of imaging techniques, including bioluminescence resonance energy transfer (BRET), fluorescence resonance energy transfer (FRET) and a newly developed technique to examine protein-protein interactions with sequential BRET-FRET imaging (termed SRET). Using these techniques, their goal is to identify D3R binding partners that are influenced by the level of DA depletion. Interaction of D3R with these newly recognized interactors might lead to its supersensitivity and influence disease in their model of PD.

doi:10.1242/dmm.005728

Disease Models & Mechanisms is interested in other graduate students and postdocs who work with models of human disease and are interested in establishing a collaboration. Applications are evaluated by the excellence of the candidate, and the importance and innovative quality of the work to be done. Preference is given to collaborations between basic researchers and clinical scientists. If you would like to apply for a DMM Travelling Fellowship, instructions and the application form are available at http://dmm.biologists.org/site/misc/fellowships.xhtml