Protein Trafficking and Neurodegenerative Disease ARC Program
Director, Dr. Lindsay Farrer,
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Recycling of the amyloid precursor protein (APP) from the cell surface via the endocytic pathways plays a key role in the generation of amyloid ß-peptide (Aß), the accumulation of which is thought central to the pathogenesis of Alzheimer disease (AD). This ARC is the outgrowth of our major discovery of association of the *SORL1* genetic variants with AD risk (*Nature Genetics* 2007;39:168-177). We also showed that *SORL1* variants may regulate its tissue-specific expression and trafficking of APP into recycling pathways. This ARC explores the role of vesicular sorting proteins and other genes involved in protein trafficking in the etiology and pathophysiology of AD and other neurodegenerative disorders. The power of this ARC lies in its ability to validate any finding using independent approaches of genetic epidemiology, cell biology, model systems and pathology. New collaborations engendered by the ARC have led to the discovery of novel associations with several genes encoding retromer and retromer associated proteins, axon guidance and wnt signaling. Many of these associations were bolstered by functional evidence supporting their connection to disease processes. ARC-related research has yielded **68 funded grants** to Boston University, Boston Medical Center and the BU-affiliated VA Hospital in Bedford, MA with annual direct costs totaling **$17.45 million** and more than 160 peer-reviewed articles. In the last year, ARC investigators received new grants with annual direct costs totaling **$4.25 million**. Efforts in the next year will be focused on continuing existing research projects, preparing multiple multi-investigator grant applications including ones to private industry, and expanding the scope of the ARC to encompass neurodegenerative diseases more generally.

As a "Graduated ARC", our focus will continue to be on our NIH-funded grants on AD in African Americans, protective mechanisms of *APOE* ε2, and new project for identifying rare variants for AD in Koreans by whole genome sequencing, as well as pursuit of new grant applications because our budget will not include support for laboratory supplies or reagents for experiments not specifically for our funded projects.

Specific aims:
Aim 1: Continue working on projects currently in progress summarized briefly below. These projects will be supported primarily by investigators' grants.
Aim 2: Prepare and submit new multi-investigator grant applications based on work carried out with previous ARC support.
Aim 3: Continue and perhaps expand the multi-disciplinary team of investigators through monthly ARC meetings and seminars including outside speakers. It is our experience that new ideas and collaborative projects are born through consistent and frequent contact among ARC members.

Participating Members

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