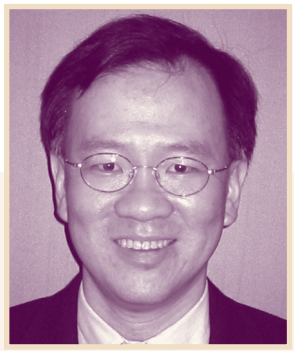
ASP—Infectious Diseases Society of America—Young Investigator Award in Geriatrics



Award Recipient:

Albert Shaw, MD, PhD
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Project:

Effects of Mutations in APP and Presenilin Associated with Alzheimer's Disease on Lymphocyte Development and Function

Mentorship Team:

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The goal of these experiments is to elucidate the consequences of mutations in the presenilin (PS) and amyloid precursor protein (APP) genes associated with early-onset forms of Alzheimer's Disease (AD) on B and T lymphocyte development and function. APP, an integral membrane glycoprotein, is subjected to a series of post-translational cleavage steps resulting in the generation of β-amyloid protein (Aβ). Mutations in APP associated with familial AD promote the generation of 42-residue isoforms of Aβ (Aβ42) that are invariably found in the brains of affected individuals. APP cleavage to Aβ is facilitated by a multi-protein complex that includes PS, and notably, mutations in either of the two PS genes (predominantly PS-1) have also been linked to familial AD.

Studies in mice carrying APP transgenes indicate that immunization against Aβ42, or administration of anti-Aβ42 antibodies, ameliorates the pathologic and behavioral changes associated with AD which ordinarily occurred in such mice. However, human trials of therapeutic vaccination were complicated by the occurrence of meningoencephalitis in some individuals, underscoring the potential importance of the immune system in AD. In this context, products of APP processing, including Aβ, are generated in lymphocytes; in addition, Aβ peptides have been shown to augment calcium mobilization in activated lymphocytes and stimulate lymphocyte proliferation in healthy individuals. Moreover, abnormalities in calcium signaling have been reported in cells from patients with mutant PS alleles, and evidence of altered calcium flux has been reported in lymphocytes from patients with both early- and late-onset AD. However, the roles of APP and PS in lymphocyte biology remain poorly understood.

To elucidate the effects of AD-associated APP proteins, we are employing retroviral-mediated gene transfer to transduce murine bone marrow with mutant APP isoform cDNAs that are expressed in lymphocytes. B and T cell populations will be analyzed in lethally irradiated mice reconstituted with transduced bone marrow. To analyze mutant APP expression in the context of preserved transcriptional and post-transcriptional regulation, an APP mutation linked to familial AD will be introduced, via gene targeting, into the endogenous murine APP locus. To study the function of PS in lymphocytes, we are analyzing mice in which an AD-associated mutation has been introduced into the endogenous PS-1 locus. Finally, we are generating radiation chimeras expressing a second PS-1 mutant in hematopoietic cells. We chose this mutant since PS-1 undergoes proteolytic cleavage and is expressed as a heterodimer; the mutant we have constructed lacks these cleavage sites and should be unaffected by potentially limiting cellular factors required for post-translational processing and stable expression of PS-1.

The developmental phenotype of lymphocytes from radiation chimera and knock-in mice will be assessed, along with immunization responses and signal transduction pathways mediating antigen receptor cross-linking, mitogenic, and pro-apoptotic stimuli. The elucidation of developmental, signaling, and antibody responses in lymphocytes carrying APP and PS mutations associated with familial AD should provide insight into abnormalities of the immune response in patients and potentially may illuminate an interface between the adaptive immune system and the pathogenesis of AD.