



2006-07 Research Grant Award Winner

Robert M. Clancy, PhD, NYU Hospital for Joint Diseases ***Molecular mechanisms of cardiac injury by anti-SSA/Ro – SSB/La antibodies***

Lay Abstract:

A serious risk factor faced by prospective mothers with Sjögren's Syndrome is that the fetus may develop congenital heart block (CHB), a permanent condition that damages heart's own internal pacemaker, resulting in an extremely slow heartbeat. CHB almost always requires a baby to have a mechanical pacemaker implanted, and can be life-threatening, with a mortality rate of nearly 20% among fetuses and newborns. We are seeking to understand, on a molecular level, how a mother's SS-related autoantibodies trigger and maintain inflammation leading to scarring and permanent damage to the fetal heart. Improved understanding of this process may eventually lead to new treatments or prevention strategies for CHB and perhaps salivary gland injury in general.

Scientific Abstract and Research Proposal:

A strong clinical association with anti-SSA/Ro-SSB/La antibodies is the development of congenital heart block (CHB) in a fetus, a serious concern facing 2% of primigravid mothers with Sjögren's Syndrome (SS). This risk is 20% in women who have previously had a child with CHB or neonatal lupus (NL) rash. WE have assembled the largest cohort to date of families with affected children, through the U.S. Research Registry for Neonatal Lupus and international collaborations, and have focused over a decade of research on neonatal lupus, integrating bench and bedside discoveries. Immunohistologic findings in cardiac sections from CHB cases support the signature lesion as exaggerated apoptosis and fibrosis. Studies have demonstrated that apoptosis provides access of extracellular maternal antibodies to normally intracellular antigens. Preliminary data support the novel concept that healthy cardiac cells are capable of clearing adjacent cardiocytes undergoing apoptosis and surface binding of anti-SSA/Ro-SSB/La antibodies inhibits this unrecognized, but vital, cardiocyte function. Accordingly, in this proposal, we will test the hypothesis that antibody-mediated "diversion" of physiologic apoptotic cell clearance is a critical initiating factor in the cascade to CHB. The experimental plan of this proposal is designed to firmly establish the phagocytic function of cardiocytes in clearing apoptotic cells and define the role of SSA/Ro and SSB/La in this process. In **Specific Aim 1**, electron and confocal microscopy will be used to identify receptor(s) and intracellular organelles that participate in the process of internalizing autologous apoptotic cardiocytes. In **Specific Aim 2**, the specificity of the inhibitory effect of anti-SSA/Ro and/or SSB/La antibodies on autologous

engulfment will be identified and pathologic consequences explored. Determination of the mechanism of inhibition by identification of ligand binding partners on the phagocytosing cardiocyte and/or consideration of steric interference will be the focus of **Specific Aim 3**. It is envisioned that results obtained in these cardiac studies will provide important insights linking apoptosis to the mechanism of other tissue injury e.g. salivary gland, by antibodies prevalent in patients with SS.