

# THE HARTWELL FOUNDATION

## 2011 Individual Biomedical Research Award

### Review of Proposed Research

**Investigator:** Mary Louise Markert, MD, Ph.D.  
**Professor**  
**Departments of Pediatrics and Immunology**

**Institution:** Duke University

**Proposal:** Use of Thymus Transplantation to Induce  
Tolerance to Liver Transplants



With more than 1800 pediatric solid organ transplants performed annually in the U.S., Louise seeks to revolutionize solid organ transplantation in children by harnessing the thymus to teach the body's T cells (specialized white blood cells that play a central role in cell-mediated immunity) to accept transplanted tissue or organs from unrelated individuals. Children receiving liver, heart or lung transplants must take medications for the rest of their lives to prevent their immune system from attacking and rejecting the transplant. These children require close medical supervision to avoid infections, tumors, kidney damage and heart disease and a high rate of rejection caused by non-compliance in taking the necessary immunosuppressive drugs. To address this unmet need, Louise proposes that tolerance can be induced to unmatched donor liver by also transplanting donor thymus, the organ responsible for T cells. The thymus also expresses the most important immunological identity molecules (major histocompatibility antigens) required to "educate" the T cells not to attack the body (avoid autoimmune disease), which is key to a balanced immune system so that it can mount attacks on invading organisms or unmatched tissue, yet is tolerant of all of the body's own tissues. In her approach, the liver recipient would undergo thymectomy and simultaneously be treated with cyclosporine and antibodies to suppress and deplete the recipient's T cells prior to liver and thymus transplantation. The donor thymus will thus facilitate the immune system to accept and tolerate the solid organ transplant, but most importantly, still be available to vigorously fight infection. The rationale for the approach is based on her research published in 2010, which reported on 60 infants born without a thymus and who received thymus transplants. Not only did T cells develop in these infants, but no drugs were needed to prevent rejection of the donor thymus. The children continued to be tolerant of the thymus from the unrelated individual. This approach would be widely applicable to children because most solid organ donors for pediatric transplants are children with a thymus that can be readily procured. Using a rat with normal immune system as an animal model, Louise intends to implant both liver and thymus from the same donor in order to demonstrate how to manifest tolerance induction. If successful, she will present a plan to the FDA to initiate patient trials to enable children to accept an organ transplant without the necessity of life-long suppression of their immune system in order to prevent rejection.