Dr. Shannon L. Meeks

First HTRS Mentored Research Award (MRA) Recipient 2007
and
First HTRS Mid-Career Research Award (MCRA) Recipient 2017

Shannon L. Meeks, MD
Dr. Meeks is currently an Associate Professor in the Department of Pediatrics at the Emory University School of Medicine in Atlanta, Georgia. She obtained a Bachelor of Science in Mathematics from Duke University. After earning her medical degree at the University of Mississippi in Jackson, she served her residency in pediatrics at the University of Virginia, Charlottesville, and pursued a fellowship in pediatric hematology/oncology at Emory University.

Dr. Meeks has a basic, translational, and clinical research interest in hemophilia and inhibitors. Her current projects focus on understanding the early stages of the immune response to factor VIII and understanding how individual profiles of inhibitor epitopes influence a patient's response to treatment with both FVIII and bypassing agents, as well as response to immune tolerance therapy. She was the first recipient of the HTRS MRA in 2007, as well as the first recipient of the newest HTRS award, the MCRA in 2017.

The HTRS MRA Program

The HTRS Mentored Research Award (MRA) Program provides financial support for qualified fellows or junior attending/junior faculty pursuing clinical, translational, or basic science research projects in hemostasis and/or thrombosis under the guidance of an experienced mentor. Since the program's inception in 2007, HTRS has awarded over $6 million for 37 Mentored Research Awards.

The goals of the HTRS MRA Program are to:

- **Combat the shortage of skilled academic physician researchers in benign hematology in North America** by providing funding, mentorship, and career development support to early stage physician scientists pursuing academic research careers in benign hematology (or areas of medicine with a major component of benign hematology).
- **Advance the science underlying the clinical management of hemostasis and thrombosis disorders** by supporting new research to improve the health and well-being of people living with these disorders.

Dr. Shannon L. Meeks was the first HTRS Mentored Research Award recipient in 2007 for her project titled: "Non-overlapping Epitopes in the C2 Domain of Factor VIII: Characterization of Structural Location, Functional Interactions, and Pathogenicity." The goals of this project were to map the structural location of three distinct

non-overlapping epitopes in the C2 domain of fVIII and to characterize the mechanism of inhibition of antibodies that recognize these epitopes using a hemophilia A mouse model. Her work was mentored by Dr. Pete Lollar. At the time of her award, Dr. Meeks was a third year Hematology/Oncology fellow at Emory University.

Dr. Meeks report on the results of her MRA-funded research:

"The antibody response to the C2 domain of factor VIII (fVIII) consists of a continuum of structural epitopes that can be divided into 2 major functional classes. The classical anti-C2 antibodies inhibit the binding of fVIII to phospholipid and von Willebrand factor (VWF). The non-classical anti-C2 antibodies inhibit the activation of fVIII by thrombin and/or factor Xa. Historically it was thought that classical C2 antibodies dominated the immune response but we have shown in my laboratory that the non-classical antibodies play a major role. The initial description of the murine response was published in 2007 (Meeks, SL et al. Blood 110:4234-42, 2007). Next a novel ELISA was developed to map the structural epitopes of polyclonal human patient plasmas. Using murine monoclonal antibodies with known epitopes we mapped the C2 antibody spectrum of 26 patient plasmas. Over half of the patients had non-classical antibodies present in their plasmas and most patients had a combination of non-classical and classical C2 antibodies. These results were recently published (Meeks, S.L. et al. Blood 112, 1151-1153, 2008). This data was presented at an invited lecture at the 2008 Gordon Conference on Hemostasis.

The pathogenicity of classical and non-classical murine anti-human fVIII monoclonal antibodies (MAbs) was tested in a murine in vivo bleeding model. MAbs were injected into the tail veins of –hemophilia A mice to a peak plasma concentration of 60 nM followed by an injection human B domain-deleted fVIII to a concentration of 2 nM. At 2 hours the mice were anesthetized and a 4 mm tail snip was made. The amount of blood lost into a collection tube of normal saline over 40 minutes was measured. 4A4 is a type I anti-A2 inhibitor with an inhibitory titer of 40,000 Bethesda units (BU)/mg IgG. I54 and 1B5 are classical type I anti-C2 inhibitors with inhibitory titers of 1300 and 930 BU/mg IgG, respectively. 2-77 is a non-classical type II anti-C2 inhibitor that produces a residual fVIII level of 40% at saturating concentrations and whose titer is 21,000 BU/mg IgG. 2-117 is a non-classical anti-C2 MAb with inhibitory activity less than 0.4 BU/mg IgG. All of these MAbs except 2-117 significantly increased blood loss over control mice injected with fVIII alone (p= 0.01-0.02, Mann-Whitney Test). The amount of blood loss was similar at these saturating concentrations of antibody despite inhibitory titers ranging from 930-40,000 BU/mg IgG. Increasing the dose of fVIII to 4 nM could overcome the bleeding diathesis produced by the non-classical MAb 2-77, but not the type I antibodies, 4A4 and I54. Similar results were seen in the in vitro Bethesda assay where 4A4 completely inhibited both 1 U/ml and 3 U/ml fVIII at saturating concentrations, while 2-77 had 40% residual activity with either 1 or 3 U/ml fVIII (0.4 U and 1.2 U respectively). These results suggest that high-dose fVIII rather than bypassing agents may be warranted in patients with an inhibitor response dominated by non-classical anti-C2 antibodies. This data was published in the Journal of Thrombosis and Haemostasis in 2009 (Meeks, S.L. et al. J Thromb Haemost. 2009, 7(4):658-664)."

Publications resulting from Dr. Meeks' MRA-funded project:

Meeks SL, Healey JF, Parker ET, Barrow RT, and Lollar P. Non-Classical Anti-C2 domain antibodies are present in patients with factor VIII inhibitors. Blood 2008, 112(4): 1151-3.

Meeks SL, Healey JF, Parker ET, Barrow RT, and Lollar P. Non-Classical Anti-Factor VIII C2 Domain Antibodies are Pathogenic in a Murine in vivo Bleeding Model. J Thromb Haemost. 2009, 7(4):658-664.

Dr. Meeks in turn has become a mentor, along with her original mentor, Dr. Lollar, to an HTRS MRA Award recipient in 2016, Dr. Glaivy M. Batsuli for her project titled "Characterizing the Immune Response to the C1 Domain of Factor VIII."

Dr. Meeks said of the MRA Program: "The HTRS MRA gave me the time to obtain enough data to successfully get a K08, provided critical funding when I was a Post-Doc, and was a stepping stone for my career as a physician scientist." (After receiving the MRA, she was able to go on to receive other awards including the K08, R21, U54 Project Leader, and the Aspire Hemophilia Award.)

The HTRS MCRA Program

Ten years later, in 2017, Dr. Meeks was the first HTRS Mid-Career Research Award (MCRA) recipient for her project titled: "Unraveling the Immune Response to Factor VIII." The goal of this project is to provide novel tools necessary to further explore the uptake and presentation of fVIII to the immune system.

Dr. Meeks summarizes her MCRA project: "Approximately 20-30% of patients with severe hemophilia will develop inhibitory antibodies to factor VIII. In my laboratory we have advanced the understanding of the immune response to fVIII through the study of fVIII structure and the spectrum of epitopes recognized by B cells and thus anti-fVIII antibodies. The ability to track antibodies and the B cells that produce them to individual epitopes that make up a patient's polyclonal response may be critical to individualizing treatment. Through this project I will develop fVIII tetramers as well as tetramers of individual domains to track fVIII specific B cells over time. The goal of the project is to provide novel tools necessary to further explore the uptake and presentation of fVIII to the immune system. The validation of these tools will provide valuable pilot data for my R01."

The HTRS Mid-Career Research Award (MCRA) Program provides financial support for mid-career investigators pursuing clinical, translational, or basic science research projects in hemostasis and/or thrombosis.

The goals of the MCRA Program are to:

- Provide financial support for talented mid-career physician-scientists to enable them to **transition from mentored research to full research independence**.
- **Combat the shortage of skilled academic researchers in benign hematology** by supporting mid-career physician-scientists in the U.S. and Canada at a critical juncture in their academic research careers. Upon the completion of a project funded by the MCRA Program, the recipient should be ready to apply for a large-scale grant to expand their research in hemostasis and/or thrombosis such as an NIH R01, NIH R34, or the equivalent from another agency such as the American Heart Association or the Canadian Institutes of Health Research (CIHR).
- **Advance the science underlying the clinical management of hemostasis and thrombosis disorders** by supporting research to improve the health and well-being of people living with these disorders in the U.S. and Canada.

Dr. Meeks Talks about Her Career Path

"I am a physician scientist with a basic, translational, and clinical interest in the immune response to factor VIII (fVIII). While finishing my undergraduate studies with a degree in Mathematics at Duke University I became interested in Pediatric Hematology during a summer internship at the Mississippi Children's Cancer Clinic.

Almost immediately solving the puzzles of coagulation fascinated me. Fast-forward 10 years and as a pediatric hematology/oncology fellow I was faced with choosing a research project. Given my mathematics background I was leaning towards getting a master's in clinical research focused on statistical challenges in rare populations. Dr. Tom Abshire who was my mentor at the time strongly encouraged me to spend at least two years in the lab of Dr. Pete Lollar to learn from a fVIII expert and to gain coagulation laboratory experience that "can only help your career in hemostasis". My first project was investigating the immune response to fVIII in a 4-year-old girl with acquired hemophilia A. I identified that she had a polyclonal immune response that had a large component directed against the C2 domain. This led me into my first big project that involved characterizing the immune response to the C2 domain. As part of that initial project I learned that the antibody epitope of the C2 domain was more important than the Bethesda titer in terms of pathogenicity in our murine model. This combined with a couple of patients in the clinic who were responding to fVIII despite having inhibitor titers well above 10 BU/ml launched my career focus to understand the immune response to fVIII and how particular antibody epitopes within the polyclonal response might influence a patient's response to treatment.

Given my very limited background in science when I entered the laboratory it was critical that I an extended period of time to develop laboratory skills, the ability to think critically, and sound scientific methodology. An initial HTRS mentored research award gave me this opportunity. I turned that award into a K08 that expanded my skills with specific training in immunology under the mentoring of Dr. Jim Zimring. Dr. Zimring's primary focus at that time was the immune response to red blood cell antigens. The combination of these grants and excellent mentoring prepared me for successful applications to the National Institutes of Health (NIH) for a R21. I also am a project leader on a U54 a multi-investigator grant. I have my own laboratory at Emory and three senior authored papers that have come out of my laboratory. Despite this success I have yet to obtain a coveted R01 and currently am a new investigator as defined by the NIH. The HTRS MCRA will provide valuable pilot data for my R01.

My career goal is to continue my multi-faceted approach to investigating inhibitors in hemophilia A by addressing questions from a basic science perspective that can ultimately lead to changes in clinical care. Throughout my career I have had at least 75% protected time for research. My clinical time is almost exclusively spent in the Comprehensive Bleeding Disorders Clinic taking care of relatively large number of patients with hemophilia and inhibitors. I was recently promoted to Associate Professor of Pediatrics."

Dr. Meeks Serves as an Example of the Success of HTRS Award Programs

Targeted career development programs, such as the HTRS MRA and MCRA Programs, are sorely needed to recruit physician scientists into research careers in non-malignant hematology and to support them with appropriate resources to grow their careers, enabling them to transition from training to mentored research to full research independence. Without such support, research with the potential to change the way we diagnose, treat, and manage non-malignant coagulation disorders in the future is seriously threatened.

Dr. Meeks is an excellent example of the success of the HTRS Award Programs to help bridge the funding gap in the various stages of non-malignant hematologists' career pathway.