

TENURE RECOMMENDATION
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL
DEPARTMENT OF PEDIATRICS AND COMMUNICABLE DISEASES

Steven W. Pipe, M.D., is recommended for the granting of tenure to be held with his title of Associate Professor of Pediatrics and Communicable Diseases, Department of Pediatrics and Communicable Diseases, Medical School.

Academic Degrees:

B.S.	1985	University of Toronto
M.D.	1989	University of Toronto

Professional Record:

2004-Present	Associate Professor of Pediatrics and Communicable Diseases, University of Michigan
1998-2004	Assistant Professor of Pediatrics and Communicable Diseases, University of Michigan
1996-1998	Lecturer, Department of Pediatrics and Communicable Diseases, University of Michigan

Summary of Evaluation:

Teaching: Dr. Pipe has been involved in undergraduate teaching from 1996 to the present time. Three former undergraduate students who trained with him are in medical school. One is a graduate student at Columbia University and another student is still currently an undergraduate. Dr. Pipe had a summer research opportunity medical student from 2002 to the present time. He has been involved in the direct training of two fellows from pediatric hematology/oncology in his laboratory. One of the fellows, Dr. Thornburg, is now a faculty member at Duke University Medical School. He has served on the thesis committee of one doctoral student and he has been involved in teaching pediatric residents and fourth-year students from 1999 through 2002. He was involved in the first-year Core Curriculum in Clinical Skills. He has taught in the second-year Core Curriculum Hematology Sequences since 2002. In 2002, he received recognition as the Outstanding Teacher of that sequence. Dr. Pipe has been awarded a training grant from the National Hemophilia Foundation for Hemostasis and Thrombosis Clinical Fellowship Training Program, making the University of Michigan one of only ten sites selected nationally for this award. Dr. Pipe has also given a number of extramural presentations locally, regionally, nationally, and internationally.

Research: Primarily Dr. Pipe has focused his research on the elucidation and the biology of Factor VIII synthesis, secretion, and activation as it relates to etiology of Hemophilia A and to providing new insights which may advance efforts related to somatic cell gene therapy for this disease. Progress in this regard has included the characterization of Hemophilia A missense point mutations leading to Factor VIII synthesis. This mechanism has been further characterized

to involve the ubiquitin-proteasomal degradation machinery. He has also determined the role of Factor VIII interaction with endoplasmic reticulum chaperones in mediating proper folding and/or of Factor VIII for intracellular degradation. These studies provide fundamental insights into the Factor VIII biosynthetic pathway and provided the foundation for future modifications of Factor VIII design to improve the efficiency of secretion. Although he worked in the laboratory of Dr. Kaufman, Dr. Pipe played the major role of carrying out the Factor VIII studies. Dr. Pipe has served as a co-principal investigator on grants held by Dr. Kaufman. His role on these grants was to write all the proposals related to Factor VIII biology. Effective October 1st of 2005, Dr. Pipe initiated his own NIH RO1 grant designed to evaluate "Factor VIII bioengineered for improved secretion efficiency and activity." Besides this grant as mentioned earlier, Dr. Pipe is the principal investigator on a national hemophilia training grant.

Dr. Pipe has also characterized a novel genetically engineered construct of the active form of Factor VIII, which has a several-fold increase in specific activity due to resistance to proteolytic inactivation. This protein has been characterized *in vitro* and studies are currently directed toward the characterization of its *in vivo* properties. This protein holds promise as an alternative product for replacement therapy in patients and as a choice of protein for gene therapy expression.

He has also carried out a series of elegant studies regarding the modification of the Factor VIII molecule. Dr. Pipe has identified that the addition of even a few asparagine-linked oligosaccharides within a short B domain spacer improves secretion of Factor VIII.

He has characterized mutations within the triplicated A domain interface of Factor VIII. His results support a role for this region in stabilizing activated Factor VIII and support the validity of a novel molecular model of the A domain of Factor VIII.

Dr. Pipe's research has been acknowledged in the past by his winning the Young Investigator Award in the Department of Pediatrics, the Young Investigator Award provided by the International Society on Thrombosis and Hemostasis as well as the American Society of Pediatric Hematology/Oncology. In 1998 he was selected as a faculty scholar of the American Society of Hematology.

As a reflection of his national recognition, Dr. Pipe has become an ad hoc grant reviewer for the Singapore Ministry of Health. He is an ad hoc grant reviewer for the National Heart Lung and Blood Institute (NHLBI) and he is a reviewer for a number of hematology and general biology journals.

Recent and Significant Publications:

Miao HZ, Sirachainan N, Palmer L, Cunningham M, Kaufman RJ and Pipe SW: Bioengineering of coagulation factor VIII for improved secretion. *Blood* 103(9):3412-3419, 2004.

Gilbert GE, Kaufman RJ, Arena AA, Miao H and Pipe SW: Four hydrophobic amino acids of the factor VIII C2 domain are constituents of both the membrane-binding and von Willebrand factor-binding motifs. *J Biol Chem* 277(8):6374-6380, 2002.

Pipe SW, Saenko EL, Eickhorst AN, Kembal-Cook G and Kaufman RJ: Hemophilia A mutations associated with one-stage/two-stage activity discrepancy disrupt protein-protein interactions within the triplicated A domains of thrombin-activated factor VIIIa. *Blood* 97:685-691, 2001.

Pipe SW, Eickhorst AN, McKinley SH, Saenko EL and Kaufman RJ: Mild hemophilia A caused by increased rate of factor VIII A2 subunit dissociation: Evidence for non-proteolytic inactivation of factor VIIIa in vivo. *Blood* 93:176-183, 1999.

Pipe SW, Morris JA, Shah J and Kaufman RJ: Differential interaction of coagulation factor VIII and factor V with protein chaperones calnexin and calreticulin. *J Biol Chem* 273(14):8537-8544, 1998.

Service: Dr. Pipe is recognized nationally by his service as a member of the National Hemophilia Foundation and the World Federation of Hemophilia. He has served on the Council of the Midwest Society for Pediatric Research and, in 2005, assumed the position of President of the Midwest Society for Pediatric Research. Since 2003, he has served as a member of the National Data Over-Cite Committee for the National Hemophilia Program. Within the Department in the Division of Pediatric Hematology/Oncology he is the Director of Pediatric Coagulation and Hemostasis. This program has grown by at least 10% per year since Dr. Pipe has taken over the program. He has become one of the most sought after pediatric investigators in this field as a lecturer and teacher. As part of his role as Director, Dr. Pipe attends clinic one day a week and he attends on the Pediatric Hematology/Oncology service four to six weeks per year.

External Review:

Reviewer A: "I think Dr. Pipe is one of the very best of physician-scientists [of his cohort] interested in coagulation research...Dr. Pipe is a scientific and clinical leader in the field of hemostasis. Dr. Pipe is highly regarded by the national and international scientific community."

Reviewer B: "Dr. Pipe's scholarship has indeed impacted the field of molecular coagulation by his thoughtful and state-of-the-art dissection of elements of the factor VIII protein which are responsible for altered secretion and synthesis and holds promise for future therapeutic strategies. Dr. Pipe has a scholarly niche within the field of pediatric coagulation in which he is one of the very few state-of-the-art cell and molecular biologists who are pediatric practicing physicians."

Reviewer C: "Clearly, Dr. Pipe is a very promising mid career investigator who will be highly sought after by various programs. There is no question that he is one of the rising stars in the field of hemophilia...Without hesitation I can say that Dr. Pipe is eminently qualified for promotion to Associate Professor with Tenure at [my institution] and I dare say at many prestigious institutions around the country."

Reviewer D: "Dr. Pipe continues to have a brilliant career and is nationally and internationally known for his work in hemophilia. He is undoubtedly at the cutting edge of research and I am confident that his insight into the biosynthesis of Factor VIII (FVIII) molecule will define hemophilia treatment in the future."

Reviewer E: "...Dr. Pipe's record shows excellence in research and teaching, with strength in service. Those qualities would undoubtedly make him an excellent candidate for promotion to associate professor with tenure at [my institution]. From a national point of view, we need good researchers in pediatric hemostasis, so it is wonderful that your institution has chosen to nurture one."

Reviewer F: "Most assuredly, Dr. Steven Pipe is a highly regarded member of both the hemophilia research and clinical community, a fact to which his long list of invited local, national and international presentations can easily attest."

Reviewer G: "...Steven Pipe will continue to develop into one of the senior physician-scientists in pediatric coagulation. Dr. Pipe currently is at the leading edge of a small group of physician researchers in his field. I see him ultimately on par with leaders in our field..."

Summary of Recommendation:

Dr. Pipe has participated in all phases of academics. He has served as an outstanding teacher in the Hematology Course for the second-year students and has been ranked as an outstanding teacher on multiple occasions. He is a sought after speaker regionally, nationally, and internationally. He has just received an NIH RO1 grant to pursue this research. He has also served as Director of the Pediatric Hemophilia and Thrombosis Program within the Division of Pediatric Hematology/Oncology. Finally, he has gained national recognition by his invitations to speak, review papers, and write chapters in books. He brings additional expertise and talent to the Division of Pediatric Hematology/Oncology and provides both important scholarly activities and needed clinical services. He has incorporated the educational mission of the Department of Pediatrics in all aspects of his work. His granting of tenure is recommended without reservation and with the highest degree of enthusiasm.



Allen S. Lichter, M.D., Dean
*Newman Family Professor
of Radiation Oncology*

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