

Division of Hemostasis and Thrombosis



Barbara Furie, PhD, and
Bruce Furie, MD,
Co-Chiefs

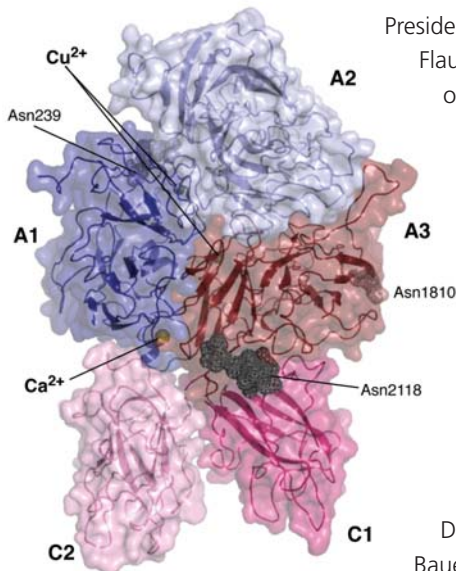
● Overview

The Division of Hemostasis and Thrombosis was formed in 2000, incorporating the Center for Hemostasis and Thrombosis Research and the Hemophilia and Thrombosis Clinical Center. This Division is focused on basic and clinical research related to blood coagulation and vascular biology, as well as clinical activities related to bleeding and thrombotic disorders. The Division includes nine faculty members.

Drs. Bruce Furie and Barbara C. Furie are Presidents of the 22nd Congress of the International Society on Thrombosis and Haemostasis which meets in Boston in July 2009. Drs. Bruce Furie and Barbara C. Furie also serve as Presidents of the International Society on Thrombosis and Haemostasis from 2007 until 2009. Dr. Kenneth Bauer is the Vice President of this congress and Dr. Robert Flaumenhaft is the editor of its state-of-the-art book. Approximately 10,000 delegates from over 80 countries are expected to attend this medical/scientific meeting.

The fifth edition of the leading textbook in hematology, *Hematology: Basic Principles and Practice*, has been completed and is now in press for publication in October 2008.

Dr. Bruce Furie is a co-editor of this text, and Dr. Barbara C. Furie, Dr. Bruce Furie and Dr. Kenneth Bauer are chapter contributors.



- Structure of Factor VIII. The X-ray crystal structure of the B-domain deleted Factor VIII was determined. This protein, absent or defective in hemophilia, has five domains. These include the A1 and A2 domains of the heavy chain and the A3, C1 and C2 domains of the light chain. Structure-function analyses are now possible by studying the location of mutations on Factor VIII that are known to be associated with hemophilia of varying degrees of severity. See Ngo et al, 2008.

● Clinical Activities

The Division maintains an outpatient specialty clinic, the Hemophilia and Thrombosis Clinical Center. Patients are seen weekly with fellows by Drs. Furie, Roth, Bauer and Flaumenhaft. This clinic represents a referral center for patients with bleeding or thrombotic disorders. Several clinical trials involved in understanding the relationship of cancer-associated thrombosis and the development of new oral Factor Xa inhibitors are closely integrated into this clinical program.

● Research Activities

Research Funding • AY'07

Federal Direct	1,132,412
Federal Indirect	528,614
Other Direct	719,651
Other Indirect	61,157

The Division moved to temporary laboratory space at 840 Memorial Drive, Cambridge, in April 2006 and returned to the new Center for Life Sciences in July 2008. The major thrust of the research interests in the Division focus within the area of hemostasis and thrombosis. Major activities in the laboratory include the study of thrombus formation *in vivo*, using novel instrumentation developed by this group for real time *in vivo* confocal and widefield imaging in the microcirculation of a living mouse. High resolution X-ray crystallographic structural studies have focused on the urokinase-urokinase receptor complex, domains of Factor VIII, and conformers of tissue factor. In addition, the molecular basis of granule secretion in platelets is under study.

● Awards and Honors

Dr. Kenneth Bauer was promoted to Professor of Medicine at Harvard Medical School. Dr.

Robert Flaumenhaft was promoted to Associate Professor at Harvard Medical School. Dr. Natalia Beglova is the recipient of a Junior Faculty Scholar Award from the American Society of Hematology. Dr. Jeffrey Zwicker is the recipient of a K23 mentored clinical investigator award from the NIH, with Drs. Furie and Bauer as his mentors. Dr. Bruce Furie gave the Desire Collen

Foundation plenary lecture at the XXI Congress of the International Society on Thrombosis and Haemostasis. He delivered plenary lectures at the XXI Congress of the ISTH in Geneva, Switzerland in 2007, the 52nd GTH Congress in Wiesbaden, Germany in 2008, the European Hematology Association meeting in Copenhagen, Denmark in 2008 and the XX Congress of the Latin American Group for Hemostasis and Thrombosis, in Buenos Aires, Argentina in 2008.

● Selected Publications

Vandendries ER, Hamilton JR, Coughlin SR, Furie B, Furie BC. PAR4 is required for maximal platelet accumulation but not fibrin generation after laser-induced vascular injury in an *in vivo* mouse model of thrombosis. *Proc Natl Acad Sci* 2007; 104:288-292.

Dubois C, Panicot-Dubois L, Gainor JF, Furie BC, Furie B. Thrombin-initiated platelet activation *in vivo* is von Willebrand factor-independent during thrombus formation in a laser injury model. *J Clin Invest* 2007; 117:953-960.

Lin L, Huai Q, Huang M, Furie B, Furie BC. Crystal structure of the bovine lactadherin C2 domain, a membrane binding motif, shows similarity to the C2 domains of factor V and factor VIII. *J Mol Biol* 2007; 371:717-724.

Panicot-Dubois L, Furie BC, Furie B, Lombardo D, Dubois C. Circulating pancreatic bile salt-dependent lipase: a role in platelet aggregation and thrombus formation. *J Clin Invest* 2007; 117:3708-3719.

Cho J, Furie BC, Coughlin S and Furie B. A critical role for extracellular protein disulfide isomerase during thrombus formation *in vivo*. *J Clin Invest* 2008; 118:1123-1131.

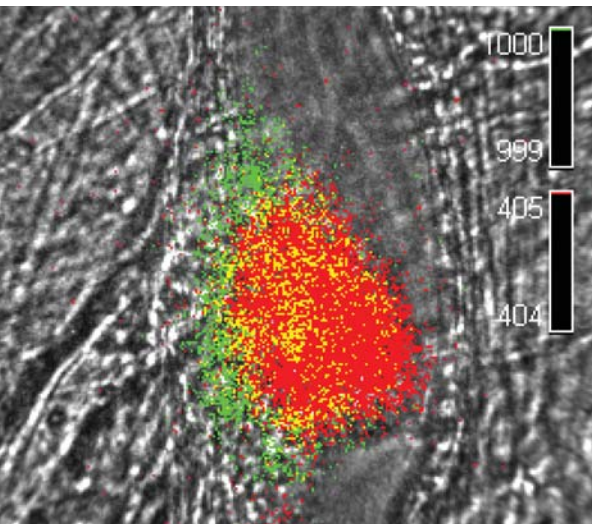
Ngo J, Huang M, Roth DA, Furie BC, Furie B. Crystal structure of human factor VIII: Implications for the formation of the factor IXa-factor VIIIa complex. *Structure* 2008; 16:597-606.

Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med* 2008; 359:938-49.

Huai Q, Zhou A, Lin L, Mazar AP, Parry GC, Callahan J, Shaw DE, Furie B, Furie BC, Huang M. Crystal structures of two human vitronectin, urokinase and urokinase receptor complexes. *Nat Struct Mol Biol* 2008; 15:422-423.

Flaumenhaft R, Rozenvayn N, Feng D, Dvorak AM. SNAP-23 and syntaxin-2 localize to the extracellular surface of the platelet plasma membrane. *Blood* 2007; 110:1492-501.

Sim DS, Dilks JR, Flaumenhaft R. Platelets possess and require an active protein palmitoylation pathway for agonist-mediated activation and *in vivo* thrombus formation. *Arterioscler Thromb Vasc Biol* 2007; 27:1478-85.



● *In vivo* expression of protein disulfide isomerase and platelets during thrombus formation in a live mouse. Protein disulfide isomerase (green) is secreted by platelets and endothelial cells following vessel wall injury. The platelet thrombus (red) that forms requires protein disulfide isomerase. See Cho et al, 2008.

● Faculty

Kenneth A. Bauer, MD	Bruce Furie, MD
Natalia Beglova, PhD	Mingdong Huang, PhD
Mark Brown, PhD	David Roth, MD
Robert Flaumenhaft, MD, PhD	Leisa Stenberg, PhD
Barbara Furie, PhD	Jeffrey Zwicker, MD