HEMOSTASIS & THROMBOSIS

Bruce Furie, MD, and Barbara Furie, PhD, Co-Chiefs — 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. The 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.

Highlights

Clinical Activities

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

Omoz Aisiku, PhD

Educational Programs

Drs. Furie and Bauer continue to lecture second-year New Pathways students at Harvard Medical School in the Hematology course. Based on lectures from this course, Professor H. F. Bunn has developed a new textbook in hematology for medical students. Dr. Furie prepared four chapters, and Dr. Bauer wrote two chapters of the book, which was recently published.

Research Activities

Major activities in the laboratory this year include the study of thrombus formation *in vivo* using novel instrumentation developed by this group for real time *in vivo* confocal and wide-field imaging in the microcirculation of a living mouse. This group has discovered the importance of extracellular thiol isomerases in regulating the initiation of blood coagulation and thrombus formation. High resolution X-ray crystallographic structural studies have focused on the urokinase-urokinase receptor complex, Factor VIII, and conformers of tissue factor. In addition, the molecular basis of granule secretion in platelets is under study.

Lotte van Hessem

Top: Sarah Kim

Selected Publications

Jasuja R, Furie B, Furie, BC. Endothelium-derived but not platelet-derived protein disulfide isomerase is required for thrombus formation in vivo. *Blood* 2010; 116:4665-74.

Zwicker JI, Trenor CC 3rd, Furie BC, Furie B. Tissue factor-bearing microparticles and thrombus formation. *Arterioscler Thromb Vasc Biol* 2011; 31:728-33.

Lin Z, Jiang L, Cai Yuan C, Jensen JK, Zhang X, Luo Z, Furie BC, Furie B, Andreasen PA, Huang M. Crystal Structure of a Michaelis complex between plasminogen activator inhibitor-1 and urokinase-type plasminogen activator. *J Biol Chem* 2010; 286:7027-32.

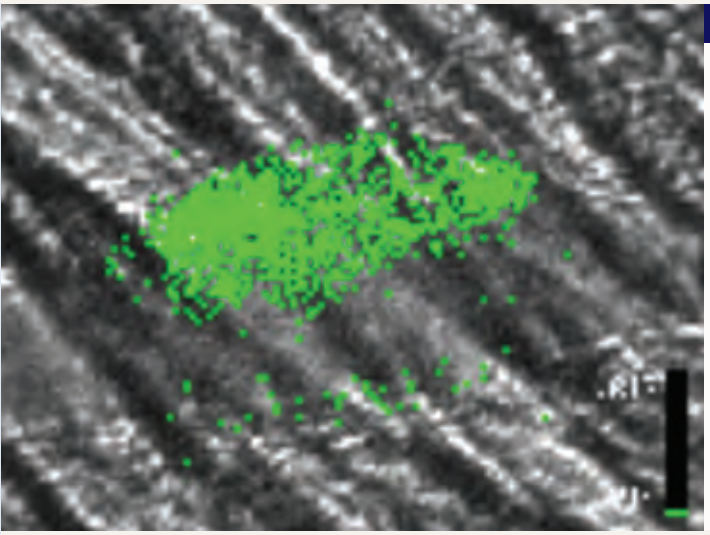
Arad A, Proulle V, Furie RA, Furie BC, Furie B. β2-Glycoprotein-1 autoantibodies from patients with antiphospholipid syndrome are sufficient to potentiate arterial thrombus formation in a mouse model. *Blood* 2011; 117:3453-9.

Kroh HK, Panizzi P, Tchaikovski S, Baird TR, Wei N, Krishnaswamy S, Tans G, Rosing J, Furie B, Furie BC, Bock PE. Active site-labeled prothrombin inhibits prothrombinase in vitro and thrombosis in vivo. *J Biol Chem* 2011; 286:23345-56.

Dowal L, Sim DS, Dilks JR, Blair P, Beaudry S, Denker BM, Koukos G, Kuliopulos A, Flaumenhaft R. Identification of an antithrombotic allosteric modulator that acts through helix 8 of PAR1. *Proc Natl Acad Sci USA* 2011; 108:2951-6.

Liu J, Gao BB, Clermont AC, Blair P, Chilcote TJ, Sinha S, Flaumenhaft R, Feener EP. Hyperglycemia-induced cerebral hematoma expansion is mediated by plasma kallikrein. *Nat Med* 2011; 17:206-10.

Kolyada A, Lee CJ, De Biasio A, Beglova N. A novel dimeric inhibitor targeting Beta2GPI in Beta2GPI/antibody complexes implicated in antiphospholipid syndrome. *PLoS One* 2010; 5:e15345.



A significant discovery this year has been that a well-known housekeeping enzyme, protein disulfide isomerase, is critically required for thrombus formation. Inhibition of this enzyme after secretion from platelets and the vascular endothelium, following injury, inhibits thrombus formation. A small molecule that inhibits protein disulfide isomerase has the potential of developing into a new drug to control pathologic thrombus formation.

Thrombus formation in a live mouse, showing protein disulfide isomerase antigen (green). Courtesy of Bruce Furie, MD, and Barbara Furie, PhD.

Honors and Awards

Bruce Furie, MD – Served as Secretary General of the International Society on Thrombosis and Haemostasis. He delivered the Sir John Dacie Memorial Lecture at Hammersmith Hospital in London UK. He was also the Shapur Naimi Lecturer and Visiting Professor in Cardiology at Tufts Medical Center in Boston and the Cardiovascular Institute Visiting Professor at Brigham and Women's Hospital in Boston. Dr. Furie was also an invited speaker at the annual meeting of the British Society of Haematology in Edinborough, Scotland.

Bruce Furie, MD, and Barbara Furie, PhD – Delivered the Roon Lecture at Scripps Research Institute, La Jolla, California.

Kenneth Bauer, MD, Bruce Furie, MD, and David Roth, MD – Named to "Best Doctors."

Faculty

Natalia Beglova, PhD
Kenneth Bauer, MD
Robert Flaumenhaft, MD, PhD
Barbara C. Furie, PhD
Bruce Furie, MD
Mingdong Huang, PhD
David Roth, MD
Jeffrey Zwicker, MD