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Neutrophil extracellular traps, scholarly debates, and public–private partnerships: highlights of the eighth annual *Platelet Colloquium*

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At the *Eighth Annual Platelet Colloquium* (Photo 1), held in Washington, DC on February 1–2, 2013, participants identified and discussed emerging paradigms of thrombosis and fertile areas of investigation for platelets and related therapeutics. Consistent with this overarching theme, the *Colloquium's* objectives were to:

- Discuss new paradigms in platelet biology and thrombosis
- Identify and discuss emerging areas of platelet-related investigation and their translation to drug development
- Outline and discuss regulatory processes and innovative grant funding opportunities for platelet-related pharmacotherapies and research

The first of the Colloquium's three main sessions included discussion of the rising importance of neutrophil extracellular DNA traps (NETs), which represent an intersection of inflammation, infection, and thrombosis. NETs, a network of DNA fibers, histones, and nuclear proteins produced by nucleosome release from activated neutrophils, are a long-recognized component of the body's innate immune response to infection. It has recently become apparent, however, that NETs form within blood vessels in response to injury and disease, providing a lattice for red cell adherence, platelet activation, and thrombus formation. Both DNAse and heparin have been shown to disrupt the NET structure, preventing thrombosis. This finding might have relevance in the development of novel therapeutic targets. In addition, the fact that polymers have been shown to bind to cell-free DNA in vitro might hold promise in the development of methods to assess thrombotic risk and status.

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Also in the first session, the *Colloquium* brought back a popular segment from 2012, a position debate between two leading researchers. This year's topic was "Is There a Role for Antiplatelet Therapy in the Management of Atrial Fibrillation?" Arguing in favor was Steven R. Steinhubl, MD, of Geisinger Medical Center, Danville, Pennsylvania; arguing against was Elaine Hylek, MD, of Boston University Medical Center. Table 1 summarizes the main points from both sides of the debate. In the end, the debaters agreed that well-controlled studies will be needed to address many of the knowledge gaps relevant to this question.

Session II contemplated the evidence regarding the use of antiplatelet therapies in several high-risk groups, with additional discussions about avenues for future investigation. Despite the available data, substantial knowledge gaps persist for the use of antiplatelet agents in persons with hemoglobinopathies, diabetes, other metabolic disturbances, previous stroke, and deep vein thrombosis. In addition, providers are uncertain about the optimal use of antiplatelet agents during transcatheter aortic valve implantation (TAVI), during "hybrid" coronary procedures, and as a bridge to noncardiac surgery.

In Session III, the focus turned to regulatory sciences and governmental support of platelet-related research. Regulatory agencies recognize that the clinical trial ecosystem in the United States is under stress (Table 2). Representatives from the U.S. Food and Drug Administration (FDA) and the National Institutes of Health were on hand to outline the roles that government agencies can play in easing these stressors and facilitating the conduct of high-level research that both addresses public health needs and meets regulatory requirements for therapeutics in the U.S. Specific examples of the new approaches and philosophies embraced by the FDA include implementing new concepts to appropriately

Photo 1 2013 Platelet Colloquium participants. *First row* (*l*–*r*): Jung H. Lee, PharmD; Dominick J. Angiolillo, MD, PhD; Susan S. Smyth, MD, PhD; Richard C. Becker, MD; Elaine Hylek, MD, MPH; Marilyn J. Telen, MD; Andrew Farb, MD. *Middle row*: Deepak L. Bhatt, MD, MPH; Harold L. Dauerman, MD; Christopher Rusconi, PhD; Jawaad Sherriff, PhD; Chao Fang, MS; Laura Haynes, PhD; Emilie Montenont, MS; W. Keith Hoots, MD; Juan Maya, MD, MS; Dave Broman, BSME. *Back row*: Bruce Sullenger, PhD; Jonathan Day, MBBS, MRCS, MFPM, PhD; John W. Eikelboom, MB, BS, MSc; Steven R. Steinhubl, MD; Dale W. Laird, BSc, MSc, PhD

Table 1 Pros and cons of using antiplatelet agents in management of patients with atrial fibrillation (AF)

Pro	Con
Antiplatelet agents are commonly used in a substantial minority of patients treated for AF	Warfarin is an established, well-characterized, efficacious, and inexpensive treatment for AF; the combination of clopidogrel and aspirin is significantly less effective at preventing stroke than is warfarin, with similar rates of major bleeding
Antiplatelet agents are probably beneficial in patients with AF when anticoagulants are inappropriate	Among persons unsuitable for warfarin, the addition of clopidogrel to aspirin therapy results in significantly fewer vascular events and strokes but significantly more major bleeding. In persons unsuitable for warfarin, apixaban offers significant benefit over aspirin in prevention of stroke or a systemic embolic event, with similar rates of major bleeding
The role for antiplatelet agents in patients with AF requiring antithrombotic therapy should be limited to those who cannot reliably maintain therapeutic anticoagulation	Treatment guidelines call for preferential use of oral anticoagulation in patients with AF who warrant preventive treatment

regulate medical devices and emphasizing benefit/risk principles throughout regulatory decision-making. Both of these aspects rely on early and continuous discussions among investigators, agencies, and research sponsors.

Public–private partnerships (PPPs) can offer a collaborative approach to achieving the disparate goals of regulatory bodies, investigators, study sponsors, payers, and patient advocacy groups. Their chief advantages are that they can maximize the benefits of very limited resources and harness divergent expertises to create inclusive, informed, and efficient research programs. Two models of PPPs were discussed during the meeting.

The first, the Dual AntiPlatelet Therapy (DAPT) study, is being conducted by an international PPP of four manufacturers of drug-eluting stents, three manufacturers of thienopyridine/antiplatelet medications, the Harvard Clinical Research Institute, and the FDA. This collaboration was formed in response to an FDA request to address an important public health question, namely: What is the optimal duration of DAPT after stent implantation? In this study, the largest randomized trial involving coronary stents, more than 26,000 patients receiving drug-eluting or bare metal stents at 450 centers who were event-free after 1 year of open-label DAPT were randomized to receive either another 18 months of DAPT or placebo. The two primary endpoints are (1) the composite incidence of all-cause mortality, myocardial infarction, or stroke and (2) the incidence of stent thrombosis, both within 33 months after beginning randomized treatment. The primary safety endpoint is the incidence of major bleeding during the same interval. Randomization was completed in August 2012, and study results are expected late in 2014.

A second example is a collaboration between the National Heart, Lung, and Blood Institute; the U.S.

Table 2 Stressors on the U.S. clinical trial ecosystem

Risk-averse environment: patients and hospitals
Weak clinical study infrastructure
Contracting
Inexperienced sponsors, sites, and investigators
Financial challenges
High costs of studies
Reimbursement delays or lack of coverage
Delays in study implementation
Regulatory requirements
Institutional review/ethics board approvals
Enrollment challenges
Restrictive selection criteria
Competing studies
Excessive time needed to complete studies

Department of Defense; academia; and industry that is taking a systems biology approach to understanding trauma-induced coagulopathy (TIC). It came together because of a lack of information about the mechanisms, optimal management, and outcomes of resuscitative strategies and trauma-related conditions in general, in both the community and military theaters. This cross-disciplinary group aims to define better (1) the natural history of TIC, in both civilian and military populations; (2) the ability to rapidly assess the state of persons who have sustained trauma; (3) tools for intervention; and (4) strategies for outcomes surveillance that extend beyond the initial intervention(s).

Finally, the *Colloquium* also continued its tradition of recognizing early career investigators who will likely have an impact in the field of platelet-related science. The *Colloquium's* Early Career Investigator Awards are designed to acknowledge the importance of focused scholarly pursuits and mentorship for scientists on an academic career trajectory in the field of platelet biology. The 2013 awardees included:

- Laura Haynes, PhD, (Photo 2) from the University of Vermont, who presented her research on the relationship between platelet-derived microparticles and the procoagulant nature of platelet-associated prothrombinase
- Chao Fang, MS, (Photo 3) of Case Western Reserve University in Cleveland (travel award), who discussed the implications for thrombosis risk of increased plasma nitric oxide and prostacyclin levels induced in genetically altered mice
- Jawaad Sherriff, PhD, (Photo 4) of the State University of New York at Stony Brook, whose poster presentation summarized the in vitro evaluation of shear-induced platelet activation in a ventricular assist device after antiplatelet therapy

Photo 2 Laura Haynes, PhD

Photo 3 Chao Fang, MS

Photo 4 Jawaad Sherriff, PhD

Each year, the *Platelet Colloquium* invites thought leaders; basic, translational and clinical scientists; and international thought leaders to discuss emerging knowledge from the intersecting fields of platelet biology, thrombosis, and hemostasis. The meeting's cochairs are Richard C. Becker, MD of Duke University Medical Center; Susan S. Smyth, MD, PhD, of the University of Kentucky, and Harold L. Dauerman, MD, of the University of Vermont College of Medicine. This year, Dr. Smyth was recognized by the *Platelet Colloquium* for her highly laudable contributions to bench science, training, education, and the translation of fundamental aspects of platelet biology to the bedside.

Next year, the Colloquium's program will focus on platelets as blood-borne messengers and reporters and the importance of philanthropy in support of scientific advances.