EVANS CENTER FOR INTERDISCIPLINARY BIOMEDICAL RESEARCH

Your ARC Title: **Thrombosis to Hemostasis (TtoH) ARC**

Abstract:

The Thrombosis to Hemostasis (TtoH) ARC brings together basic and translational research towards understanding thrombosis secondary to organ pathology. *While studies of primary thrombosis (owing to platelet/vessel malfunction) have been extensively investigated, our proposed ARC is unique in that it opens new focus on mechanisms of organ-induced changes in thrombosis and vascular hemostasis, and consequent complications.* Thrombosis resulting in cardiovascular and cerebrovascular events is the number one cause of death in the world and also contributes to severe morbidity in toxin-mediated diseases. Thrombosis is a complex process, which lies at the intersection of several of disciplines and epitomizes the essence of a multidisciplinary approach not only to gain deeper understanding of its pathogenesis but also for developing novel personalized predictive tools and therapeutic targets. Leveraging the experience of PIs in the fundamental components of thrombosis, the TtoH ARC proposes to examine the novel mediators (metabolites and proteins secreted by a diseased organ) of thrombosis identified by the BU investigators. Once considered as innocent bystanders retained in renal failure, emerging data indicate prothrombotic properties of some of the metabolites in patients of renal failure. Indole metabolites (indoxyl sulfate and indoxyl acetate) have been recently identified as inducers of tissue factor and enhancer of thrombosis. Lysyl oxidase (LOX) is an extracellular copper enzyme that is released from cells and initiates the cross-linking of collagen and elastin in fibrotic organs (kidney included), and now found to have an unexpected role as a potent regulator of thrombosis.

The central hypothesis of this proposal is that the newly identified mediators (proteins/metabolites) evoke thrombosis during organ pathology, as well as following systemic influence of infectious pathogens. The following translational and mechanistic aims will provide initial guides for examining this **central hypothesis**.

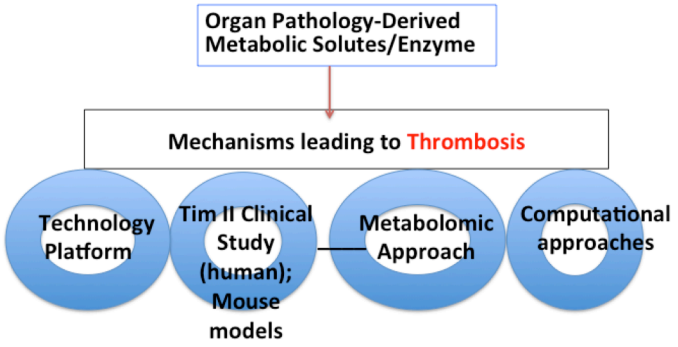
Aim 1 leverages a unique resource provided to this ARC by NHLBI (*following a reviewed application*) of 501 samples from Thrombosis in Myocardial Infarction-II (TIMI-II) trial. The trial examined coronary angioplasty after tissue plasminogen activator therapy in myocardial infarction (MI) patients and documented post-angioplasty thrombosis presenting as reocclusion and/or reinfarction in 114 of TIMI-II subjects. Within this large cohort, 117 subjects had chronic kidney disease (CKD), which is expected to elevate levels of indole metabolites. We will examine the hypothesis that the indole metabolites and LOX levels (which we found by ELISA to be present in human serum) correlate with post-angioplasty thrombosis in TIMI-II samples, thereby serving as potential biomarkers. **1.1** correlates these mediators with post-angioplasty thrombosis. **1.2** Machine learning, an emerging branch of mathematics, will be leveraged to develop a predictive comprehensive thrombotic signature for an individualized risk score from TIMI-II set. We feel that this brings quite a *novel and progressive* perspective to such analyses.

Aim 2 addresses the cause-and-effect aspect of our quest. It examines the hypothesis that metabolites released from a pathological organ (i.e., indol metabolites) enhance thrombosis *in vivo*. New in vivo models produced here will become assets shared with our whole thrombosis community.

Aim 3 leverages novel small models of thrombotic microangiopathy to examine the hypothesis that prothrombotic metabolites augur a bad prognosis following systemic infection. **Aim 3.1** is designed to identify the conditions necessary to induce toxin sensitivity in endothelial cells and will examine the regulators of prothrombotic phenotype, including metabolites studied in Aim 1. **Aim 3.2** focuses on toxin-induced coagulopathy to examine the metabolic-thrombotic axis in vivo.

Integration of proposed Aims: Aim 1 is the translational arm of the proposal, and aims 2 and 3 develop novel animal models of thrombosis: one focused on a specific organ (kidney disease) and the other on systemic organ failure induced by infection. Novel data validating in human and animal models newly identified metabolic markers of organ pathology-induced thrombosis will be aided by complementing, interdisciplinary expertise of pathologists, biochemists, clinicians, biomedical engineers, a biostatistician, and mathematicians (**Figure 1**). Further, the ARC will provide a platform for advanced technologies (existing and newly developed by the ARC) to enable ARC members and other BU faculties to leverage novel animals models developed by the ARC, and biomarkers to aid their research. Machine learning technique will serve as a platform to develop *predictive fingerprint* for other disorders, a method of risk stratification to tailor the treatment, an essence of personalized medicine. Finally, this ARC presents a **unique opportunity** for BU researchers to jump start novel projects with collaborations of members of the New England Megakaryocyte/Platelet Club, including investigators from different hospitals affiliated with Harvard Medical School (see section A). Placing BU on this research map increases our "research visibility" and opportunity for interdisciplinary discovery and funding in this newly evolving research area of organ pathology-induced thrombotic complications.

Figure 1: New Interdisciplinary Approaches Drive our TtoH ARC



Faculty:

Members	Rank	Departments/school affiliation	Email
Katya Ravid* *ARC co-Director*	Professor of Medicine and Biochemistry, Director, Evans Center	Departments of Medicine and Biochemistry (member of Northeastern Megakaryocyte/platelet club)	kravid@bu.edu
Vipul Chitalia* *ARC co-Director*	Assistant Prof of Medicine	Internal Medicine/Renal section (member of Northeastern Megakaryocyte/platelet club)	vichital@bu.edu
Deborah Stearns-Kurosawa* *ARC co-Director*	Associate Professor of Pathology and Laboratory	Department of Pathology (member of Northeastern Megakaryocyte/platelet club)	dstearns@bu.edu
Elaine Hylek* *ARC Advisor of Translational Research*	Professor of Medicine	General Internal Medicine	ehylek@bu.edu
Janice Weinberg* *ARC Advisor of Stat Analysis*	Professor; BU School of Public Health	Department of Public Health and Department of Medicine	janicew@bu.edu
Naomi Hamburg*	Associate Professor of Medicine	Cardiology/ Medicine	nhamburg@bu.edu
James Hamilton	Professor of Physiology and Biophysics	Physiology & Biophysics	jhamilt@bu.edu

Joyce Wong*	Professor of Biomedical Engineering	Biomedical Engineering	jwong@bu.edu
Jean Francis	Assistant Professor of Medicine	Internal Medicine/Renal section	Jean.Francis@bmc.org
Richard Cohen	Professor of Medicine	Internal Medicine/Cardiovascular Division	racohen@bu.edu
Francesca Seta	Assistant Professor	CVI; Medicine	setaf@bu.edu
Quillen, Karen	Associate Professor of Pathology and Laboratory Medicine/Associate Professor of Medicine	Internal Medicine/Hematology-Oncology	Karen.Quillen@bmc.org
Daniel G. Remick Jr.	Chairman and Professor of Pathology and Laboratory Medicine	Department of Pathology	remickd@bu.edu
Susan Leeman	Professor of Pharmacology	Department of Pharmacology	sleeman@bu.edu
George Murphy	Assistant Professor of Medicine	Internal Medicine/Hematology-Oncology (member of Northeastern Megakaryocyte/platelet club)	gjmurphy@bu.edu
Vijaya Kolchalama*	Principle Member of Technical Staff	Machine Learning and Computational Modeling Division, Draper Laboratory, MIT	vbk@mit.edu
Shinichiro Kurosawa*	Associate Professor of Pathology and Laboratory Medicine	Department of Pathology	kurosawa@bu.edu
Anqi Zhang	Research Instructor	Medicine/ endocrinology	anqi@bu.edu
Sibji Sarkar*	Assistant Professor of Medicine	Medicine/Cancer Center	Ss1@bu.edu
Hannah Bader	Instructor of Medicine	Hem/Onc	baderh@bu.edu
Members of the Megakaryocyte/Platelet Club, such as Drs. Joseph Italiano, Alan Cantor	Associate Professor of Medicine/BWH	Harvard Medical School (members of Harvard-BU Megakaryocyte/platelet club)	jitaliano@rics.bwh.harvard.edu Alan.Cantor@childrens.harvard.edu

(*) Denotes Core Faculty who have or will be actively participate in the ARC-funded projects. **Note**: not all ARC members are expected to be directly involved in projects selected for a particular year, and for which the majority of funding will be needed.