SUMMARY OF MEETING PROCEEDINGS

INTRODUCTION

The Trans-Agency Coagulopathy in Trauma Workshop was convened on April 5–7, 2010, to develop recommendations of research directions/solutions to overcome the critical barriers to discovery and translation of new products for the diagnosis and management of coagulopathy.[1] The Workshop format emphasized cross-disciplinary discussions to identify the challenges and limitations in the current practice of coagulopathy diagnosis and treatment, gaps in the state of knowledge of coagulation and coagulopathy biology, and solutions to rapidly advance the research to develop new diagnosis and treatment measures.

The Workshop was attended by more than 130 experts representing the National Institutes of Health (NIH), Department of Defense (DoD), Centers for Disease Control and Prevention, U.S. Food and Drug Administration, Department of Veterans Affairs, academia, and industry. Countries represented at the Workshop included Australia, Canada, Israel, the United Kingdom, and the United States. This document summarizes the proceedings of the Workshop.

OPENING REMARKS

The meeting was opened by Dr. Andrei Kindzelski, Medical Officer and Program Director, Division of Blood Disease and Resources (DBDR), National Heart, Lung, and Blood Institute (NHLBI), NIH. He welcomed everyone, briefly reviewed the Workshop goals and introduced Dr. Susan Shurin, Director of the NHLBI. Dr. Shurin noted that this is a tremendous opportunity to work on the problem of coagulopathy in trauma. She commented on the potential that existed at the Workshop for cross-talk and cross-fertilization of ideas. She also emphasized the importance of working jointly and collaboratively to address the biological and translational research opportunities.

Dr. Keith Hoots, Director of the DBDR, NHLBI, welcomed everyone. He highlighted a natural history study on coagulopathy in head trauma conducted 30 years ago at the University of Texas Medical School at Houston, which showed a validated coagulation score as well as diminished antithrombin levels to be good predictors of mortality in the period within 4 hours of injury. He commented that the trauma community needs to examine the biology of head and systemic trauma in the context of vascular injury and to determine whether improved biologic predictors of survival and recovery can be found for therapeutic decision making.

Subsequently, Dr. Joseph Palma, Senior Scientific and Medical Advisor to the U.S. Army Medical Research and Materiel Command (USAMRMC) and The Surgeon General, welcomed all attendees. He emphasized that systems biology approaches to understanding the etiology and progression of disease have been successfully applied in other fields, and integrative research promises to generate new knowledge that will lead to the development of new products.

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[1]Coagulopathy is defined as a clinically significant maladaptive response of the clotting system including its biochemical components as well as platelets and endothelium. In practice, it refers to an excessive tendency to bleed although it could refer to an excessive tendency to clot.

Dr. Kenneth Mann, Professor of Biochemistry and Medicine at the University of Vermont and Chair of the Workshop, commended the NHLBI and USAMRMC for organizing the Workshop in a display of true intergovernmental cooperation. He provided an overview of trauma and coagulopathy, highlighting his and others' research on developing better procedures for the diagnosis and therapeutic intervention of hemorrhagic and thrombotic diseases. He noted that there needs to be (1) an opportunity in both the military and civilian communities to develop a natural history of coagulopathy in trauma, (2) the ability to rapidly assess the state of an individual who has experienced trauma, (3) tools for intervention, and (4) outcomes surveillance that exceeds the initial intervention of the surgical team (since the most likely consequence of surviving a coagulopathic state will be the generation of a thrombotic state).

METHOD

Day 1 – Presentations

The first day of the Workshop consisted of a series of 16 presentations by scientists who are studying various aspects of coagulopathy in trauma (see Appendix A, Meeting Agenda) and the application of systems biology approaches. A broad array of research topics was covered, ranging from basic coagulation biology to stochastic modeling of blood coagulation to the clinical management of coagulopathy after trauma.

Day 2 – Working Groups

On the second day of the meeting, participants divided into four Working Groups: Biology, -omics, Animal Models, and Diagnostics/Biomarkers. Three Co-Chairs facilitated the discussions in each Working Group. Co-Chairs for each Working Group are shown in **Table 1**.

Table 1. Working Group Co-Chairs

Working Group	Basic Science Co-Chair	Clinical Science Co-Chair	Systems Biology Co-Chair
Biology	Chuck Esmon	Gilbert White	Lee Hood
-omics	David Galas	David Pinsky	Rasha Hammamieh
Animal Models	Karim Brohi	John Holcomb	Frank Doyle
Diagnostics/Biomarkers	John Griffin	Nigel Key	Scott Diamond

Participants were charged with answering several questions during the Working Group sessions, based on their expertise and the material presented on the first day of the meeting. Specifically, they were asked to:

- Identify the knowledge gaps related to the network biology of coagulation and trauma coagulopathy. For each gap, identify specific research questions that, if successfully answered, would help close the knowledge gap.
- Identify the advanced technologies (e.g., systems biology tools) necessary to accelerate research for the analysis of biological networks and the identification of diagnostic and therapeutic targets.
- Define the critical barriers to discovery and translation of new products for the diagnosis and management of coagulopathy. Define specific recommendations to overcome each barrier and more quickly advance basic research into lead product or strategy development.

Following the individual Working Group discussions, the entire Workshop membership reconvened, and one Co-Chair from each Working Group briefed their group's conclusions. Open discussion followed each of the Working Group Co-Chairs' briefings. There was considerable overlap in the broad themes presented by the Co-Chairs.

Day 3 – Integration Session

The Workshop Chair, Working Group Co-Chairs, and Workshop organizers (NHLBI and DoD) met for a closed session on the third day of the meeting to synthesize information generated by the Working Groups and formulate the findings and recommendations presented in this summary.

FINDINGS/RECOMMENDATIONS

At the start of the integration session, Dr. Mann proposed that the group develop a series of broad objectives followed by more detailed descriptions of research related to coagulopathy induced by trauma to define the critical questions and to identify potential approaches to discovering novel diagnostic, prognostic, and treatment strategies.

Some meeting participants expressed their uncertainty about the name of the disorder. Following an open discussion, the term "trauma-induced coagulopathy" (proposed in the 2010 publication by Bouillon et al.[1]) was accepted by majority consensus.

Trauma-Induced Coagulopathy (TIC)

Injury is one of the leading causes of death in the world. Recently, it has been recognized that some severely injured patients exhibit an early and profound maladaptive response of their entire coagulation and inflammation systems. This TIC has multiple etiologies and contributes measurably to both early and late morbidity and mortality in trauma patients.

The natural history of TIC and the consequences of current interventions are poorly described and require exploration at multiple levels extending from clinical to basic science, and incorporate a comprehensive systems biology approach. Research investigations should address the extent and localization of clinically relevant dysregulated hemostasis caused by sustaining substantial injury to body tissues and the vascular system. Contributing factors include: hypoperfusion, microcirculation (both local and remote), nature and extent of injury, timing of events, and loss of localization of coagulation and inflammatory cascades.

Meeting participants subsequently identified four broad objectives:

- Define the phenotypes of TIC and elucidate the underlying mechanisms.
- Provide well-defined injury models of TIC.
- Identify and validate global and specific biomarkers to address clinical and discovery needs.
- Develop new and improved interventions for the management of TIC and its consequences.

Details on each of these objectives, as developed by meeting participants, are presented on the following pages.

[1] *J Trauma*. 2010 Jan;68(1):225-30.

Phenotyping TIC and Elucidating Underlying Mechanisms

As traumatic injury occurs in a background of genetic and environmental variation, extent and site of injury, variations in treatment regimens, and temporal evolution of sequelae, it is essential to define the phenotypes of TIC. A comprehensive approach toward understanding mechanisms underlying TIC, as well as developing rapid diagnostics and treatments that can guide therapies to improve outcomes, should include the following elements.

Defining Phenotypes of TIC

TIC should be phenotypically characterized based on rigorous clinical definitions, including the first hour situation as well as early (hours), intermediate (days), or late (weeks) situations and responses to early surgical and resuscitative therapeutic interventions. Such a consistent vocabulary or set of descriptors (ontology) is required to create a comprehensive natural history of the physiological processes following trauma at both the phenomenological and mechanistic levels. Resuscitative measures including immediate surgical interventions as well as type and quality of blood products, crystalloids/colloids, pharmacological therapies, the genetic background, and the age and sex of the patients are important elements to consider. The dynamic nature of evolving coagulation defect and inflammatory activation state as well as clinical condition should be considered. As a part of this investigation, it is important to understand the quality and use of blood products in relation to an overall resuscitative strategy.

Understanding the Systems Biology of TIC

- Traumatic injury results in activation of a number of pathways and networks, both in the physiome as well as at cellular and subcellular levels. As injury evolves from a coagulation defect to an inflammatory defect, it is essential to understand the nexus between coagulation and inflammation. This includes understanding cross-talk within and between cells (intracellular networks and cell-cell interactions) and between the immune system and the coagulation system. Understanding the early phases of coagulation defect, as well as the conversion from hemorrhagic/coagulation diathesis to inflammatory diathesis to prothrombotic state over time following trauma could facilitate development of novel diagnostic and therapeutic strategies.
- Local hemostasis is essential in trauma; however, systemic thrombosis or a hemorrhagic diathesis that occurs following severe trauma can be deleterious. It is essential to understand the transition from localized to systemic coagulation/thrombosis (i.e., local control of thrombosis, loss of localization that occurs in TIC, and distal effects as they relate to evolution of the trauma phenotype). The elements that contribute both to the hypo- as well as hyper-coagulation states need to be defined. Understanding the nature of the conversion between disparate coagulation states is essential, as is the development of rapid (nearly immediate) biomarkers to detect the states and the transitions.
- Attributes of injured or inflamed tissues can contribute to early or later injury in trauma. It is essential to understand which cells are involved in TIC, including their phenotypes and outputs. To do so, it is necessary to consider the activation state of cells, including how products released from cells affect local coagulation and inflammation, as well as send signals elsewhere. Whether actively secreted by viable cells or passively released by ruptured cells, subcellular products for analysis include but are not limited to microparticles, microRNA, DNA, and proteins. Understanding the cascade of activation events is also essential for understanding TIC, including cellular contents released as danger signals.

- The physiome as it applies to trauma needs to be understood. The physiological response to trauma should be characterized by studying important organism phenotypic elements (e.g., age, gender, genetic background, and environmental factors) including interactions of whole organism physiology (e.g., temperature, pH, blood pressure, and cardiac output), circulating blood components (e.g., cellular and humoral), organ-specific functions, and local vascular biophysical properties such as shear stress and diffusion gradients.
- Understanding the microbiome as a modulator of response to trauma may also be an important topic for investigation, including not only the skin microbiome but the pulmonary and gastrointestinal microbiome as these may modulate the systemic response to trauma.
- As TIC can vary between individuals, it is important to understand the heritability of factors influencing TIC, the level of attributable risk, and gene modifiers. Understanding the genetic background of individuals can affect multiple systems involved in TIC and lead to personalized interventions and therapy.

Providing Well-Defined Injury Models of TIC

Developing Effective Cell and Animal Models of TIC

Effective cell and animal models of TIC are needed wherein injury stimuli are directly related to TIC. Research should provide the scientific community with well-defined injury models to conduct systems biology analyses of networks and potential novel biomarkers and/or to accelerate the development of novel coagulopathy products.

Characterizing TIC in Multiple Species and Comparing Across Species

As noted above, phenotypes of human coagulopathy associated with trauma are not well characterized. The phenotypes characterized in humans should be characterized similarly in multiple species (e.g., mice, rats, rabbits, pigs, dogs, and nonhuman primates). The rationale for doing so is to develop/improve models relevant to human TIC.

Fundamental biochemical mechanisms underlying coagulation of relevance to TIC have not been characterized across relevant species so that species-specific variations in response can be understood and equivalency of responses across those species can be demonstrated.

Developing Effective Computational Models

Computational models can be used to translate knowledge gained in one species to other species and ultimately to humans. They can also enable amalgamation/integration of varied clinical data input sets to prognosticate and guide therapy. The construction of computational models will require a systems biology approach to integrate large-scale datasets resulting from high-throughput experiments (e.g., genomic, proteomic, lipidomic, metabolomic, transcriptomic, and glycomic) using validated markers and assays. The resulting network models can be probed for biomarkers that indicate disease progression, as well as points of intervention for therapeutic strategies. It was noted that there is not a single monolithic model but rather a spectrum of modeling strategies and (mathematical) classes.

Identifying and Validating Diagnostics/Biomarkers Relevant to TIC

Global and Specific Biomarkers to Address Clinical and Discovery Needs

Research is needed to discover and validate global and specific biomarkers that address critical needs in trauma care such as:

- Predicting when and how much each patient will transition between hypo- and hyper-coagulopathy.

- Predicting or measuring extreme risk scenarios, disease severity, or complications.
- Identifying optimal treatment options as a patient's condition progresses with time.

Additionally, unbiased and large-scale exploration of biomarkers should examine the relevant components at the molecular, cellular, organ, and network levels. Biomarkers could include physiological and pathophysiological signatures, cellular patterns, and biophysical or molecular attributes.

Monitoring the Progression of TIC
Since TIC evolves over time and is affected by interventions, there is a need to develop global and specific biomarkers for use during time-evolving and treatment-specific clinical progression over the entire course of treatment. This includes the concept of field-deployable tests. Biomarkers should improve patient classification, predict patient progression and risks, and identify appropriate patient treatment options.

Diagnostic Technologies
There is a need to develop advanced point-of-care (POC) technologies that are accurate and rapid (< 2 to 10 min. readout), clinically relevant, user-friendly, user-independent, and clinically standardizable across many clinical centers. Such technologies may provide multiple readouts and may utilize advanced chip, microfluidic, nanotechnology, single cell, or advanced genomic technologies. Advanced technologies should therefore be developed for the in vivo assessment of local tissue trauma, organ function, or endothelial and platelet function.

Registry and Repository – Informational and Clinical Sample Archives to Drive Biomarker Discovery
An information framework should be developed to address database needs associated with:

- Developing a registry with full patient histories and well-annotated (time-stamped) therapeutic interventions.
- Establishing a repository of high-quality biosamples prepared for optimal use in genomic, proteomic, metabolomic, and glycomic studies.
- Achieving full annotation of sample preparation.

Such databases and repositories will require the ontological standardization of phenotype definitions, clinical history, sample preparation, sample analysis, and procedures for maintaining individual subject anonymity. Biorepositories will also require the development of POC tools for rapid, hands-off processing, stabilization of small blood samples, and standardized mechanisms for access.

<u>Developing New and Improved Interventions/Therapies for Managing TIC</u>
TIC is highly associated with major morbidity and mortality in patients through dysregulated hemostasis and the consequences of subsequent activation of the inflammatory, hormonal, cardiovascular, neurological, and reticuloendothelial systems. Current interventions for the management of TIC and its sequelae are not specifically targeted to the needs of trauma patients and have limited evidence to guide their use.

Therefore, new and improved interventions for the management of TIC and its consequences are needed. Research investigations should be conducted with timely approaches and should broadly address needs for the improved understanding of the utility of existing interventions, the optimization or modification of existing therapeutics, the discovery of new targets for drug discovery, and the development of new therapeutics and new therapeutic strategies.

Elements of Research for New and Improved Interventions

- Understand the qualities and variability of the best applications of currently available blood products, biologics, therapeutics, and other interventions in the management of TIC and its sequelae. Goals of the studies will include (1) defining clinically detectable characteristics of patient populations to enable the selective administration of existing interventions for optimal patient benefit and (2) optimizing the administration of existing interventions, including timing and dosage, for each patient population. Conducting these studies will require improved monitoring and diagnostics tools, which may also be needed to implement the resulting evidence-based clinical practices.
- Improve the efficacy of currently available interventions through innovation, modification, and optimization based on prospective clinical research. Research investigations should include patient-targeted or otherwise improved blood component therapy for TIC. Products from these investigations may include clinical protocols or decision-support tools to treat massive hemorrhage.
- Identify, characterize, and understand new targets for drug discovery and clinical intervention. Research studies should investigate the biology and mechanisms of TIC, including mechanisms relevant to pre-trauma patient characteristics, the trauma event itself, and the evolution of intersecting coagulation and inflammatory cascades after trauma, as described previously.
- Develop and validate appropriately characterized models with directed applicability to TIC and/or its consequences to support biological target identification, drug discovery, and therapeutic development and evaluation, as described previously.
- Develop and evaluate novel interventions for the management of TIC and its consequences. Novel interventions may include new blood-derived products and new therapeutics. In addition, decision support tools should be developed to optimize patient treatment regimens.

Actionable and Integrated Research

Panel members described the need for actionable research or product-oriented research that integrates basic, preclinical, and clinical studies. They felt that research should address the four broad objectives (described above) in a parallel manner, not sequentially, except when a product developed under one objective is required for another objective.

The consensus view reflecting the high enthusiasm of panelists for new research advocated multiple approaches to accomplish the four broad objectives related to TIC, including: (1) establishing integrated research groups composed of clinical, preclinical, and basic scientists or a series of integrated research groups and (2) establishing individual investigator-initiated and small business research projects that can apply novel technologies and creative experiments to advance these broad objectives. Major research efforts of both large integrated research groups and of individual investigators are critical to overcome the barriers to discovery and translation of new products for the diagnosis and management of TIC.

CLOSING REMARKS

Dr. Kindzelski closed the meeting by thanking everyone for participating, noting that this is the first step in an amazing journey. Dr. Mann thanked Drs. Hoots and Palma, noting that the Workshop would not have been successful without their encouragement. Dr. Palma thanked everyone for attending and for providing the intellectual capital that money cannot buy.