Nanomedicine in Thrombosis and Hemostasis

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Preface

Nanomedicine in Thrombosis and Hemostasis: The Future of Nanotechnology in Thrombosis and Hemostasis Research and Clinical Applications

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This special issue of *Seminars in Thrombosis and Hemostasis* (STH) is dedicated to the emerging role of nanotechnology in thrombosis and hemostasis. The contributing authors highlight a range of nanoparticle systems, their applications as well as design considerations to enable clinical translation. The STH readership is thus encouraged to consider nanomedicine in thrombosis and hemostasis and think about how the increasingly successful preclinical proof-of-concept studies can be advanced to achieve real products for the benefit of patients who suffer from some of the most devastating diseases.

The field of nanomedicine is developing fast with some remarkable preclinical achievements so far.[1,2] Research activities in the field have increased significantly thanks to substantive investments by governments, universities, and the private sector, with numerous emerging companies focusing on nanotechnology. However, similar to other fields, clinical translation is a complex task requiring extensive small-animal testing as well as nonhuman primate models to provide a solid foundation for long-term advancements.[3]

Nanomedicine involves the design, manufacturing, and testing of materials at the nanometer-scale for diagnosing and treating disease in ways that are typically not possible with small molecules, antibodies, or other means. These requirements could be increased diagnostic power (e.g., imaging signal strengths), high drug payload and/or response to biological triggers (e.g., drug release in the presence of thrombosis).[4]

Sun and Sen Gupta[5] start this special issue of STH with a broad overview of vascular nanomedicine highlighting the current status as well as the opportunities and challenges. They outline the currently known cellular and molecular targets relevant in vascular disease as well as major therapeutic design strategies, with a specific focus on the comparison between active versus passive clot-targeting mechanisms.

One area where nanomedicine has made an early impact is molecular imaging using clinically well-established modalities such as ultrasound and magnetic resonance imaging (MRI).[6] The paper by Rix et al[7] in this issue focuses on ultrasound and the use of microbubbles for the diagnosis and treatment of cardiovascular diseases. After introducing the underlying physical principles of contrast-enhanced ultrasound, the authors also discuss the emerging theranostic (in combination with therapy) applications of ultrasound. Several particles-based ultrasound agents are approved for clinical use and despite some setbacks over the years, the safety of ultrasound, widespread use of scanners in nearly every major hospital, as well as the low cost of this imaging modality, make microbubble-enhanced ultrasound a very attractive field.[8]

Another well-advanced particle system is iron oxide nanoparticles for the imaging and therapy of atherosclerosis, which is the focus of the contribution by Talev and Kanwar.[9] Initially developed as a supplement to treat iron deficiencies, iron oxide particles are excellent contrast agents for MRI as well as the emerging modality of magnetic particle imaging.[10] The authors cover the diagnostic application also in

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combination with other modalities when multimodal agents are generated.

Over the last decade, the nanotechnology field has rapidly expanded, and several agents have been developed to tackle what is seen by many as the holy grail of cardiology: the identification of unstable atherosclerotic plaques. These and other recent advances are the focus of the contribution by Larivière et al,[11] which gives an extensive overview of the newest developments. The authors describe how physiological processes that have changed due to the underlying plaque inflammation can be harnessed for disease detection and also compare active versus passive nanoparticle targeting the plaque components. One of the main advantages of nanoparticle-based systems compared with other approaches is that they can be designed to respond intelligently to chemical, physical, or biological stimuli. Several of these triggers (shear, sound and light) are introduced by Qu and Ding[12] in the context of thrombolysis.

The subsequent two papers review the potential of nanomedicine to tackle the deadliest manifestation of cardiovascular disease[13]: acute thrombosis leading to myocardial infarction and stroke. The contribution from Landowski et al[14] describes the expanding research into the use of nanoparticles to treat ischemic stroke and limit the impact of the ischemia on the brain. The authors make a case for the use of nanotechnology in the diagnosis and management of stroke with a particular focus on the potential in neuroprotection. The paper also critically reviews the safety and limitations of nanomaterials in vivo. The next paper by Palazzolo et al[15] also focuses on the delivery of thrombolytic drugs in the context of acute thrombosis and how antibody-targeted particles can improve the safety and efficiency of nanomedicine with the focus on myocardial infarction.

As in other fields, the in vitro applications of nanotechnology are the fastest to translate and the use of micro- and nanotechnology has already demonstrated high utility to investigate fundamental biology and diagnose disease.[16] Once a system has shown increased sensitivity or specificity over gold standard tests or can provide new features it will then be approved by regulatory authorities.

One persistent challenge when handling a non-Newtonian liquid such as blood is how the (nano)material used influences and can impact diagnostic results and reproducibility. The contribution by Szydzik et al[17] takes a closer look at the current design consideration for such laboratory-on-chip systems and how hemocompatibility can be ensured. The authors review the current materials used and outline ways to improve performance through surface modifications and coating. They also include the hemocompatibility of the device operations as well as optimal sample preparation. Lastly, they focus on platelets as the most abundant blood components in the context of device hemocompatibility. Platelets are extremely sensitive to any form of mechanical manipulation, so maintained physiological platelet parameters are a very useful readout for high device hemocompatibility.

Similar considerations are applicable for in vivo applications; however, these are far more challenging given the exponentially higher complexity of the in vivo environment. The in vivo interaction of nanoparticles with various biological layers is an intensive area of research because the absorption of biomolecules changes the physiochemical properties of the material leading to unexpected behaviors.[18]

The final contribution in this issue of *STH* by Saha et al[19] outlines the design considerations and assays the regulatory bodies assess when approving materials for human use. The authors highlight the considerations for a rational nanoparticle design to ensure the best hemocompatibility possible. Furthermore, the work reviews a battery of assays required by regulatory bodies to move nanomaterials through the approval process such as assessing hemolysis, thrombogenicity, cardiotoxicity, inflammation, and complement activation.

As the interactions between nanomaterials and blood can have impact on toxicity, tissue interactions, and ultimately the elimination from the body, more rational approaches are emerging. One initiative named MIRIBEL ("Minimum Information Reporting in Bio-nano Experimental Literature")[20] has recently been launched to implement standards on the characterization and reporting of nanomaterials including details of the experimental protocol used. It is expected that this will help to advance the field further along the translational pipeline to the benefit of patients with serious diseases.

We trust that this special issue will be of high interest for our readers who want to familiarize themselves with the latest developments in the field of nanomedicine in thrombosis and hemostasis.

We would like to express our deep gratitude to all authors for their wonderful contributions leading to this special issue. We would also like to thank the Editor-in-Chief of *STH*, Emmanuel Favaloro, for his generous support, guidance, and allowing us to work on this exciting special issue.

Conflict of Interest
None.

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