

Conference Call

Blood-Biomaterial Interactions

by Ilya Reviakine and Robert Latour

Interactions between biological systems and artificial materials have been intensely studied over the last several decades by an interdisciplinary group of scientists combining expertise in (surface) chemistry, physics, and biology [1 and refs. therein]. Nowhere are the limitations of our understanding of the underlying mechanisms more apparent than in the case of vascular implants that interact with blood and other surrounding tissues. Examples of such implants include stents, grafts, mechanical heart valves, and ventricular assist devices (VADs). Millions of stents are implanted in patients annually world-wide; hundreds of thousands of heart valves; thousands of VADs. All of them cause life-threatening thrombotic and inflammatory complications that are managed by clinicians pharmacologically through systemic administration of anticoagulation and/or antiplatelet therapies (ACT/APT) based on drugs such as warfarin, aspirin, clopidogrel, prasugrel, etc. Alarming, thrombotic and inflammatory complications persist in patients on ACT/APT, while their systemic administration brings the danger of hemorrhagic complications necessitating close patient monitoring. With the prevalence of cardiovascular diseases on the rise and the aging of the population, the problem is only poised to become more severe, and the need for a solution—more acute [2-6].

Failure to produce a hemocompatible material for vascular implants, or to offer a reliable protocol for in vitro predictive material hemocompatibility testing, is well-recognized and has been widely discussed in the literature [2-4, 6]. Over the last several decades, it led to the diminishing interest of clinicians and funding agencies in the material hemocompatibility research.

Recent years have seen significant advances in the understanding of coagulation, thrombosis, and platelet functions; interactions between hemostatic and inflammatory cascades and the role these interactions play in the adverse reactions to materials; and the role of platelets in non-hemostatic, regenerative processes. These advances allow the examination of the material hemocompatibility problem in a new light and open new avenues of investigation. This prompted several of us to organize a series of blood-biomaterial interaction conferences with the goal of bringing together clinical, academic, and industrial researchers working on the problem and reinvigorating the material hemocompatibility field. Their focus is on understanding the underlying mechanisms as the means to further advances. The first one took place in 2014 in Frejus,



France. The second meeting in the series, **2017 Blood-surf**, took place in Clemson, SC, USA in September 2017 with IUPAC program support in New Directions in Chemistry. A sequel is planned for 2020. In this report, we briefly summarize key aspects of the 2017 meeting. Details can be found in the recent *Opinion* paper based on the meeting [6] and the earlier review [4].

The key highlights of the 2017 meeting include presentations by the clinicians, Eugene Langan (Greenville Health System, SC, USA) and Lawrence “Skip” Brass (University of Pennsylvania, USA). The former set the stage by drawing attention to the problems with the existing arterial grafts in patients who receive ACT/APT and articulating the unmet clinical needs. The latter presented clinical cases of patients with hyper- and hypocoagulable states, highlighting the difficulties encountered by clinicians needing to introduce devices (catheters) into such patients as a part of the treatment, and discussed recent developments in the clot topology and regulation of platelet activity in the forming clot.

Interactions between coagulation, inflammation, and complement systems, introduced by Maud Gorbet (University of Waterloo, Canada), formed a strong theme throughout the conference. There is recognition that while platelets are the key players in response to the materials, they are not the whole story.

A similarly recurring topic focused on standardization of hemocompatibility testing and measurements discussed by several speakers. Progress that was made *vis-à-vis* the most recent revision of the ISO10993-4 standards was discussed by Mike Wolf (Medtronic, USA). Yet, much remains to be done on the side of donor variability, anticoagulation standardization, and other testing aspects. Here, the FDA, represented at the meeting by Qijin Lu (who received no financial support from the meeting to avoid potential conflicts of interest), needs to play a greater role in the standardization efforts, but there are many variables that remain poorly understood; hence the research community is expected to make progress that would form the basis of informed decisions by regulatory agencies such the FDA. A significant advance in this direction

was presented by Steffen Braune (Helmholtz-Zentrum Geesthacht, Germany), who discussed their recent (double-blind) round-robin study of platelet adhesion to various biomaterials comparing several different laboratories [7]. Funding agencies, take note: more studies of that type are sorely needed in all the aspects of material hemocompatibility research; not only testing, but also mechanistic studies. On one hand, a concrete conclusion emerged from the discussion of standardization: anticoagulants used in the blood-bio-material interaction studies need to be titrated in a donor-specific manner based on the measurements of coagulation system activity in the specific donors. On the other hand, inconsistencies continue to plague the interpretation of results: while Buddy Ratner in his talk highlighted the history of positive experience with the hydrophobic, perfluorinated materials in vascular implants, the work of Steffen Braune suggested the opposite. The resolution of this apparent contradiction must await the emergence of reliable parameters predicting *in vivo* material performance from *in vitro* tests. The need for such parameters was discussed by various speakers, as was the need to develop proper negative controls for *in vitro* testing and some basic guidelines for developing *in vitro* tests. These include the focus on surface- and solution-phase reactions, as already shown by Kusserow [8], and on various aspects of coagulation, inflammation, and complement systems. High-throughput, microfluidic, multiparametric testing methods combined with systems-based data interpretation, championed by Scott L. Diamond (University of Pennsylvania, USA), appear to provide a useful approach for mechanistic investigations of materials, while computational tools become indispensable once one moves from materials to complex implants, as highlighted in the talk by Ali Azadani (University of Denver, CO, USA).

Different strategies for developing actively anticoagulant surfaces were presented by John Brash (McMaster, Canada) and Hitesh Handa (University of Georgia, USA). Last but not least, the topic of protein adsorption at surfaces of various materials—one with a long history—was revisited and extensively discussed. There is an acute need for developing a database of proteins adsorbed on different materials and correlating the composition of the protein layers to the biological responses, as well as for further mechanistic studies in the spirit of those presented by Chris Siedlecki (PennState, USA) and Robert Latour (Clemson, USA). See also further discussion in refs. [4] and [6].

The meeting also included a session on new methods, where in particular the biological applications of

time-of-flight secondary ion mass spectrometry (ToF-SIMS) were presented by Lara Gamble (University of Washington, Seattle, USA) [9] presentations by post-docs and young faculty members, a poster session with students' poster presentations and awards, and a round-table discussion where further steps, including the plans for the 2020 meeting, were discussed.

Bloodsurf2017 achieved its original goal: to bring together clinicians and researchers working on hemocompatibility. The meeting received strong support from NIH and IUPAC, Clemson University, industry, and societies such as the ISTH and AVS. The proposal for the 2020 was enthusiastically met by the participants, signaling renewed interest in hemocompatibility problem of bright young minds.

References:

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Ilya Reviakine <reviakin@uw.edu>, from University of Washington, Seattle, WA and Robert Latour, from Clemson University, were co-organizers of Bloodsurf2017.