



**Final report** for the 74<sup>th</sup> IUVESTA workshop, Focus on the Blood-Biomaterial Interface: Surface Analysis meets Blood Compatibility.

**Organizers:**

Chair Ilya Reviakine (KIT, Germany),

Co-Chairs

Giacomo Ceccone (EU-JRC, Italy), Miguel Manso (Madrid, Spain), Morgan Alexander (Nottingham, UK), Anouk Galtayries (Chimie ParisTech/SFV, France)

**Location:** Villa Clythia, Fréjus, France

**Web:** [www.vide.org/Bloodsurf/](http://www.vide.org/Bloodsurf/)

IUVESTA divisions: Biointerface Division

**Summary:**

The 74<sup>th</sup> IUVESTA workshop that took place in Fréjus, France, from 3 till 7 November 2014, focused on the interactions between blood and biomaterials. Millions of implants, made of a variety of materials, are implanted in patients, or used outside the patient but get into contact with the patient's blood, every year. Examples include stents, vascular grafts, heart valves and ventricular assist devices, dental implants, dialysis tubing, heart-and-lung machine membranes, oxygenator membranes, catheters and guidewires. All of these materials, without exception, activate the body's defense systems when they come into contact with the blood, causing thrombosis and inflammatory response. These are mitigated pharmacologically. Indeed, the single most important development that permitted wide-spread use of implants is that of the antiplatelet therapy in the late 1990s. Some fifty-old years of materials biocompatibility research has not yielded a breakthrough design of a material that minimizes adverse reactions, or a predictive *in vitro* test that would allow screening of potential material designs. As a result of this lack of progress, the interest in the field from clinicians and funding agencies diminished. The field is in a dire need of a new direction. The goal of the workshop was to critically evaluate the state-of-the art and discuss new directions. In that regard, the workshop succeeded masterfully, with excellent presentations spanning the past, the present, and the future of blood-compatibility research, a round-table discussion where ideas and questions were exchanged, and a poster session where early stage researchers had the chance to present their work and discuss it with the experts in an open and friendly, but rigorous, atmosphere.

## Highlights:

Conference attendees appreciated the good balance between formal presentations and critical discussions of the problems that are hindering the understanding of blood-biomaterial interactions. Particularly interesting was the realization that, when used in vitro flow studies, blood loses its activity very quickly within less than a couple hours while *in vivo* blood remains active for much longer times, even considering the regeneration cycles of various cells and proteins. Something is obviously missing in our *in vitro* studies, which if solved, may greatly enhance our ability to do longer term flow studies to address other important blood compatibility questions. On the other hand, participants remarked that this conference represented a unique possibility to hear about the various state-of-the-art approaches to surface modification being applied by leading groups in attempts to inhibit platelet and blood coagulation responses.

## Program (Figure 1) and Participants (Figure 2):

The program was carefully balanced to achieve the goals of the workshop: to critically evaluate the state-of-the-art in the blood-biomaterial interface field, surface analysis from the perspective of blood-biomaterial interactions, and discuss new research directions in these areas. The schedule included ample time for discussion, both after each talk and a dedicated “round table” session on Thursday, November 6<sup>th</sup>.

The workshop brought together 33 scientists from 11 countries (France, Germany, Italy, Portugal, Spain, Switzerland, UK, The Netherlands, plus Australia, Canada & USA) with representatives from academia, national laboratories and industry.

Appropriately, the workshop started with a lecture by Buddy Ratner *Biosurface Musings from 42 Years of Blood Compatibility Research*. The lecture provided a comprehensive overview of the field seen through the eyes of one of its key pioneers. The talk both laid the foundation for many of the concepts discussed later in the meeting and set the right tone for the entire meeting—a balance between critical review of existing concepts, questions, and problems on one hand, and a forward outlook on the other. Prof. Ratner (Seattle, USA) pointed out a number of pitfalls that continue to besiege scientists working in the field, such as futile attempts to measure material biocompatibility by looking at platelet adhesion only. Key role of platelets in response to biomaterials was introduced, as was the need for standardization of the biocompatibility studies across laboratories. Platelets and their interactions with biomaterials were later discussed in detail by I. Reviakine (Karlsruhe, Germany), while their interactions with leukocytes were discussed by Claudia Spierling (Dresden, Germany).

The second talk of the meeting addressed the issue of standardization head-on. Michael F. Wolf (Medtronic, USA) discussed the most recent work within the framework of the ISO 10993-4 standard for testing medical device interactions with blood, including the need for systematic round-robin studies and what is being done to organize them. At the moment, such studies are notoriously difficult to fund. The issue of testing was echoed throughout the meeting: Stephen Braune (Teltow, Germany) talked about methodologies they developed, and a design of a multi-center study attempting a systematic assessment of biomaterial thrombogenicity, Wim van Oeveren (Haemoscan, The Netherlands) focused

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on different flow systems for studying the effect of shear on blood-biomaterial interactions, Maud Gorbet (Waterloo, Canada) described a systems approach to *in vitro* biomaterials testing, and Hans Peter Wendel (Tuebingen, Germany) talked about *in vivo* tests and challenges involving correlating their results to those of the *in vitro* ones.

Another thread running through the meeting was focused on surface analysis. Both the contribution of surface analytical techniques to understanding protein adsorption at surfaces, blood interactions with biomaterials, and implant performance, and new techniques/developments in the surface analysis field were discussed: Dave Castner (Seattle, USA), another pioneer in the field of surface analytical studies of biomaterials, gave an overview talk with a particular focus on the secondary ion mass spectrometry; Surface analysis of biomaterials was further discussed by Anna Belu (Medtronic, USA); Robert Latour (Clemson, USA) presented a unique perspective on the conformational changes in adsorbed proteins, Tobias Weidner (Mainz, Germany) discussed sum-frequency generation spectroscopy—one of the more recent additions to the surface analytical arsenal—for studying protein adsorption; applications of non-linear optical techniques were further discussed in a contributed talk by Geraldine Rohman (Villetaneuse, France) ; Anouk Galtayries (Paris, France) discussed combinations of *ex-situ* and *in-situ* techniques for studying blood-biomaterial interface; Francesca Baldelli (Milan, Italy) discussed protein adsorption on nanoparticles and the effect of adsorbed proteins on the interactions between nanoparticles and cells; while Mathew Brown (Zürich, Switzerland) presented the latest developments in characterizing interfaces in liquid with X-ray photoelectron spectroscopy.

Surface modification and surface design topics were addressed by John Brash (Hamilton, Canada) and Manfred Maitz (Dresden, Germany), who combined anti-fouling strategies with the generation thrombin inhibitors at biomaterial surfaces; Peter Kingshott (Hawthorn, Australia), who talked about surface modification using colloidal crystals; and Dmitri Petrovykh (Braga, Portugal), who focused on model studies of peptide-surface interactions.

Early career researchers (Laura Lopez, Sinan Muldur, Paola Pellacani, Chloe Rodriguez, Sergey Shityakov, Valentina Spampinato) had a chance to present posters and 3 min blitz presentations about their research. The posters covered a range of topics in surface analysis and modification, including plasmonics and sensor design concepts. (see poster list in Annex C)

#### **AWARDS (Annex D)**

A panel of three invited speakers, namely John Brash, Bob Latour, and Claudia Sperling, chaired by A. Belu (Biointerphases editor) was involved in judging the young researchers presentations and the posters

The best poster award (750\$), offered by Biointerphases J., was presented to Paola Pellacani (Universidad Autonoma de Madrid, Spain) for her work on "Local analysis of adsorption kinetics through devices based on plasmonic enhanced Au cavity arrays"

A second award of 250\$ for young scientist Honorable Mention, was given to Taranjit Singh (University of Nottingham, UK) for his talk entitled “High Throughput Strategy for the Discovery of Next Generation Medical Devices”.

A discussion between conference participants took place on the evening of the last day. The focus of the discussion were the lessons learned from the past 50 years of research, unresolved questions preventing optimal biocompatible material design and implementation, and future strategies. One prominent topic of discussion was, once again, the development of systematic testing strategies and the parameters that are appropriate to use for the testing of blood-biomaterial interactions. A general consensus appears to be that a minimum of five parameters, one for each of the key pathways involved in adverse reactions of blood to biomaterials—platelets, leukocytes, complement, hemolysis, and coagulation—are required. Appropriate positive and negative controls are also lacking. Discussion then revolved around the design of such systematic studies (the need to involve human blood and measurement of the baseline parameter values prior to biomaterials testing were the two key points).

To summarize the message of the entire conference in a few words: we do not possess sufficient knowledge about the mechanisms behind the changes that occur in the blood once it is extracted from the body. This pertains both to its interactions with foreign materials (*e.g.*, tubes used to store the blood that was extracted) and the autoactivation of the coagulation pathways. As a result, any *in vitro* biomaterial testing is a race against time, and any measurement occurs on the background of the “noise” that arises from the autoactivation processes. This issue has never been appropriately addressed in biocompatibility studies, and represents an interesting new direction.

Finally, an important strategic question facing the field is how to rekindle the interest of clinicians in the topic of blood-biomaterial interactions. What can our community do for the clinic? Firstly, a concerted effort to include clinician partners in our discussions and studies must be made. Secondly, the studies need to be designed, keeping in mind the need of the clinicians to know which of the systems the particular material activates, and to which extent. This information would then allow them to choose an appropriate therapeutic regimen. This direction is quite different that the predominant focus of the past fifty years on minimizing non-specific interactions and platelet adhesion at biomaterial surfaces. In regards to re-initiating the dialogue with clinicians, I. Reviakine and R. Latour are currently organizing Bloodsurf 2016, a meeting that will take place in Boston in September 2016 in conjunction with the Platelets 2016 meeting and will include a joint session between the two meetings, bringing together the clinical and the biomaterials community.

#### **Outlook:**

We consider that the 74th IUVSTA workshop, *Focus on the Blood-Biomaterial Interface: Surface Analysis meets Blood Compatibility* was an important milestone in the development of the blood-biomaterial interaction field. New ideas and new directions that came out of the presentations and discussions, organization a future conference in 2016, and a special issue of the *Biointerphases Journal* are the fruits of our effort—an effort which would have been absolutely impossible without the financial support of

IUVISTA and other sponsors: SFV, KIT, Biolin/Q-sense, IONTOF, 7<sup>th</sup> framework Marie Curie program  
ThinFace, Kratos Analytical, and Plasmore, BioInterphases Journal, and Mec Wins.



**74th International IUVSTA Workshop**  
Focus on the Blood-Biomaterial Interface:  
Surface Analysis meets Blood Compatibility

November 2-7, 2014 - Fréjus, France

Last update: 12<sup>th</sup> November 2014

**Final program**

Mon. 3 November		Tue. 4 November		Wed. 5 November		Thu. 6 November	
7:00				<b>Breakfast</b>			
8:30		<b>I. Roulet</b> Platelets and their role in reaction to biomaterials		<b>J. Brash</b> blood compatible surfaces: concerning blood-material interactions.		<b>M. Goblet</b> Taking a systems approach to in vitro hemocompatibility testing of biomaterials	
9:30		<b>R. Lelour</b> Molecular Mechanisms Governing Platelet Response to Biomaterial Surfaces as a Function of Adsorption-Induced Protein Unfolding.		<b>Coffee break</b>		<b>A. Gallayries</b> Probing model blood-surface interactions by ex situ and in situ surface analyses.	
10:00		<b>T. Weidner</b> Protein interfacial structure and dynamics probed by SFO spectroscopy				<b>Refreshment</b> Possibilities of haemocompatibility testing by in vitro flow loop systems.	
11:00						<b>Refreshment</b> Prediction of the hemocompatibility of blood contacting devices according to ISO 10993-4: Chances and pitfalls	
12:00	<b>Introduction</b>			<b>Lunch</b>			
14:45	<b>B. Ratner</b> Biosurface Maturity from 42 Years of Blood Compatibility Research						
15:00		<b>M. Brown</b> X-ray photoelectron microscopy from liquid solutions for the study of small biomolecule adsorption to nanoparticles.		<b>A. Vito</b> Surfaces analysis of biomaterials.			
16:00	<b>Michael F. Wolf</b> Current Interpretation of the ISO 10993-4 Standard on Medical Device Blood Interaction Testing: The Need for Viable In Vitro Methods in the 21 <sup>st</sup> Century.			<b>Tarunjit Singh</b> A High Throughput Strategy for the Discovery of Next Generation Biomaterials			
16:30		<b>Coffee break</b>					
17:00	<b>P. Kingshott</b> Surface Modification of Biomaterials with Colloidal Crystals.	<b>Claudia Sperling</b> Influence of activated leukocytes on blood coagulation activation by biomaterials					
17:30		<b>Geralline Röllman</b> Insight in the interactions between biomaterials by nonlinear optical microscopy		<b>Coffee break</b>			
18:00		<b>D. Y. Petrovskh</b> Affinity and Reversibility of Protein-Surface Interactions		<b>Ilankov Maliz</b> Feedback controlled antiaggregant hydrogels with response to differential coagulation cascade			
18:30				<b>F. Boidin</b> Organization of the biosens interface-Relevance of the protein corona to nanoparticle interactions with the cell surface.			
19:00		<b>Flash Poster presentation (Oral / poster)</b>				<b>Round Table discussion &amp; Meeting Summary</b>	
20:30		<b>Dinner</b>					
21:30-22:30		<b>Poster session</b> Lunch: • Sven Müller • Peela Palluram • Anand Kulkarni • Chait Rodriguez • Sergey Shlyakov • Valentina Spampinato				<b>Conference Dinner</b>	
							<b>DEPARTURE</b>



**Annex A: Sponsor list**

**IUVSTA, International**

**Biolin Scientific, Sweden**

**Kratos Analytical, United Kingdom**

**Mec Wins, Spain**

**AIV, Italy**

**SFV, France**

**ION TOF, Germany**

**Plasmore, Italy**

**European Commission (Marie Curie Thin Face Programme) International**



## **Annex B: List of invited and contribution talks**

### **Invited**

B. D. Ratner, (University of Washington, Seattle, US)

**Biosurface musings from 42 years of blood compatibility research**

P. Kingshott (Swinburne University of Technology, Hawthorn, Australia)

**Surface modification of biomaterials with colloidal crystals**

I. Reviakine (KIT, Germany)

**Platelet and their role in reaction to biomaterials**

R. Latour (Clemson University, South Carolina, US)

**Molecular mechanisms governing platelet response to biomaterial surfaces as a function of adsorption induced protein unfolding**

T. Weidner (Max Plank Institute, Dresden, Germany)

**Protein interfacial structure and dynamics probed by SFG spectroscopy**

M Brown (ETH Zurich)

**X-ray photoelectron spectroscopy from liquid solutions for the study of small biomolecule adsorption to nanoparticles**

J. Brash (McMaster University, Hamilton, Canada)

**Blood compatible surfaces: controlling blood material interactions**

S. Braune (Helmholtz-Zentrum Geesthacht, Teltow, Germany)

**Hemocompatibility testing of biomaterials approach for a multi-center assessment of thrombogenic surfaces**

W. van Oeveren (Haemoscan, Groningen, The Netherlands)

Possibilities of hemocompatibility testing by in vitro flow loop systems

A. Belu (Medtronic, Minneapolis, US)

**Surface analysis of biomaterials**

F. Baldelli-Bombelli (Politecnico Milan, Italy)

**Organization of the bionano interface-relevance of the protein corona to nanoparticle interactions with the cell surface**

D. Castner (University of Washington, Seattle, US)

**The role of surface analysis in hemocompatibility studies**

M. Gorbet (University of Waterloo, Canada)

**Taking a systematic approach to in vitro hemocompatibility testing of biomaterials**

A. Galtayries (ENSCP/Chimie Paristech, Paris, France)

**Probing model blood-surface interactions by ex situ and in situ surface analyses**

H.P. Wendel (University Hospital Tuebingen, Germany)

**Preclinical testing of the hemocompatibility of blood contacting devices according to ISO10983-4-  
Chances and pitfalls**

#### **Contributions**

##### ***Affinity and Reversibility in Peptide-Surface Interactions***

D. Y. Petrovykh *et al.*

International Iberian Nanotechnology Laboratory (INL), Braga, Portugal

##### ***High Throughput Strategy for the Discovery of Next Generation Medical Devices***

T. Singh *et al.*,

Laboratory of Biophysics and Surface Analysis, School of Pharmacy, University of Nottingham, UK

**[Honorable Mention Award]**

##### ***Insight in the interactions of proteins/polymer-based biomaterials by nonlinear optical microscopy***

G. Rohman *et al.*,

Université Paris 13, Sorbonne Paris Cité, Laboratoire CSPBAT, CNRS (UMR 7244), Villetaneuse, France

##### ***Influence of activated leukocytes on blood coagulation activation on biomaterials***

C. Sperling,

Leibniz-Institut für Polymerforschung Dresden e.V., Max-Bergmann-Zentrum für Biomaterialien Dresden, Germany

##### ***Current interpretation of the ISO10983-4 standard on medical devices blood interaction testing-The need for the validation in vitro methods in the 21<sup>st</sup> century***

M. F. Wolf

Medtronic, Minneapolis, USA

##### ***Feedback controlled autocoagulation hydrogels with response to different steps of the coagulation cascade.***

M. Maitz *et al.*,

Leibniz-Institut für Polymerforschung Dresden e.V., Max-Bergmann-Zentrum für Biomaterialien Dresden, Germany

## Annex C: List of Posters

### ***Local analysis of adsorption kinetics through devices based on plasmonic enhanced Au cavity arrays.***

P. Pellacani<sup>1,2</sup>, A. Frangolho<sup>1</sup>, S. Giudicatti<sup>3</sup>, F. Marabelli<sup>3</sup>, A. Valsesia<sup>1,4</sup>, G. Marchesini<sup>1</sup>, M. Manso<sup>2</sup>

<sup>1</sup> Plasmore Srl, Ranco, Italy

<sup>2</sup> Universidad Autonoma de Madrid, Departamento de Fisica Aplicada, Madrid, Spain

<sup>3</sup> Università degli Studi di Pavia, Dipartimento di Fisica, Pavia, Italy

<sup>4</sup> EC-JRC\_IHCP, Italy

**(BEST POSTER)**

### ***Surface analysis of functionalized carbon based nanomaterials for bio-applications***

Valentina Spampinato (a), Silvia Giordani (b), Giacomo Ceccone (a)

(a) Institute for Health and Consumer Protection (IHCP), Joint Research Center, European Commission, Ispra (VA), Italy

(b) Istituto Italiano di Tecnologia Smart Materials, Italy

### ***Towards allergen & allergy diagnostics based on imaging nanoplasmatics technology***

L. Lòpez-Sanchez<sup>1,3</sup>, A. Frangolho<sup>1</sup>, P. Pellacani<sup>1,6</sup>, A. Valsesia<sup>2</sup>, W. Haasnoot<sup>3</sup>, C.S. Nielsen<sup>4</sup>, G.

Marchesini<sup>1,5</sup>

<sup>1</sup> PLASMORE SRL, Italy, <sup>2</sup> EC-JRC\_IHCP, Italy, <sup>3</sup> RIKILT-Institute of Food Safety, The Netherlands, <sup>4</sup> Schafer-

n, Denmark, <sup>5</sup> Biospher, United Kingdom, <sup>6</sup> Universidad Autonoma de Madrid, Departamento de Fisica Aplicada, Madrid, Spain

### ***Anti-fouling and cell repellent coatings produced by plasma polymerization of diethylene glycol dimethyl ether for biological and sensing applications***

Sinan K. Muldur, Radoslaw Bombera, Andrea Valsesia, Valentina Spampinato, Giacomo Ceccone,

Agnieszka Kinsner-Ovaskainen, Pascal Colpo, François Rossi

Institute for Health and Consumer Protection (IHCP), Joint Research Center, European Commission, Ispra (VA), Italy

### ***Humidity effects at the organic/porous silicon sensor interface***

C. Rodriguez, M. Manso-Silvan, V. Torres-Costa, N. Naveas

Universidad Autonoma de Madrid, Departamento de Fisica Aplicada, Madrid, Spain

### ***In silico predictive model to determine vector-mediated transport properties for the blood-brain barrier choline transporter***

S. Shityakov, C. Förster

Department of Anaesthesia and Critical Care, University of Würzburg, Würzburg, Germany

## Annex D: Workshop award winners

### AVS Biointerphases Young Scientist Award Winners



The 74th International IUVSTA Workshop, Focus on the Blood-Biomaterial Interface: Surface Analysis meets Blood Compatibility was held November 3-7, 2014 in Fréjus, France. AVS and Biointerphases were proud to sponsor Young Scientist Awards. Congratulations to these fine young scientists selected from amongst several excellent presentations!

#### First Prize

Paola Pellicani

Plasmore, srl, Ranco, Italy and Universidad Autonoma de Madrid, Spain

"Local analysis of adsorption kinetics through devices based on plasmonic enhanced Au cavity arrays"

#### Honorable Mention

Taranjit Singh

University of Nottingham UK

"A highthroughput strategy for the discovery of next generation biomaterials"