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Meeting Report

# Interface Biology of Implants

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**Implants are widely used in various clinical disciplines to replace or stabilize organs. The challenge for the future is to apply implant materials to specifically control the biology of the surrounding tissue for repair and regeneration. This field of research is highly interdisciplinary and combines scientists from technical and life sciences disciplines. To successfully apply materials for regenerative processes in the body, the understanding of the mechanisms at the interface between cells or tissues and the artificial material is of critical importance. The research focuses on stem cells, design of material surfaces, and mechanisms of cell adhesion. For the third time around 200 scientists met in Rostock, Germany for the international symposium "Interface Biology of Implants." The aim of the symposium is to promote the interdisciplinary dialogue between the scientists from the different disciplines to develop smart implants for medical use. In addition, researchers from basic sciences, notably cell biology presented new findings concerning mechanisms of cell adhesion to stimulate research in the applied field of implant technology.**

Medical implants play a growing role in routine clinical practice. In addition to replace or stabilize injured tissue permanently or transiently, the application of implant materials to stimulate the regeneration of tissue is becoming a challenge in the field of regenerative medicine. The use of implant materials is based on the idea that biomaterials function not only as mechanical support for cells and tissue but also provide a matrix to induce signal transduction in the cells that control complex molecular mechanisms responsible for proliferation und differentiation. In this context, the interface between artificial materials and living cells or tissue is an exciting field of great scientific interest and constitutes one of the most dynamic and expanding field in science and technology. Progress in this field is mainly driven by the fundamental importance for clinical applications. The research is characterized by a multidisciplinary collaboration between physics, engineers, biologists and clinicians.

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In May 2009, for the third time after 2003 and 2006 around 200 scientists met in Rostock-Warnemünde for the symposium "Interface Biology of Implants" to discuss biointerface processes at a fundamental level. The main goals of this symposium are to simulate the interdisciplinary dialogue between scientists of the different disciplines and to introduce current knowledge of basic research in cell biology and material science into the applied field of implant technology. The programme was organized in invited presentations of 20 internationally renowned scientists and complemented by short talks of mostly young scientists selected from the submitted abstracts. In addition, 80 posters presented latest results in this multidisciplinary field.

The symposium was opened with a keynote lecture presented by Hartmut Hildebrand (Lille). He gave an overview about the 7,000 years old history of application of implant materials. Rare photographs were shown which demonstrated that in these early times prostheses mainly made from metallic materials were used to restore teeth, extremities and the skull of the human body. These old documents stressed the historical relevance of medical application of implant materials.

The symposium on two days was composed of four sessions covering the interdisciplinary research in the field. The session "Stem cells and biomaterials" discussed the biological response and signalling mechanism of stem cells in the interaction with a material surface. The session "Bioactivation of implant surfaces" focussed on the tailoring of surfaces to control the cell physiology. To stimulate the field by recent data in basic cell biology, talks were presented in the third session, dealing with molecular mechanisms involved in cell adhesion. A special session dealt with the role and mechanism of controlling cells by mechanics.

## Stem Cells and Biomaterials

Research in regenerative medicine is mainly driven by the field of stem cells. In vivo these cells are located in a stem cell niche and factors in the microenvironment which involve cytokines and cell-cell as well as cell-extracellular matrix interactions determine the fate of the cells. Scientists try to understand the molecular mechanisms of controlling proliferation and differentiation into multiple directions of these cells. The control of stem cells by characteristics of a material surface constitutes an ambitious aim in the field of

implant technology. Concerning basic mechanisms in stem cell regulation, Bassem Abdallah from the laboratory of Moustapha Kassem (Odense) could identify a new factor, named Dlk1/FA1 which controls differentiation and proliferation of mesenchymal stem cells. It encodes a transmembrane protein which belongs to the Notch family. Overexpression of this protein inhibits differentiation into the main mesenchymal cells which was associated with the release of a number of inflammatory cytokines.[1] In estrogen deficiency, increased serum levels of Dlk1/FA1 were found which inhibit bone formation.[2] Mouse models demonstrated that this protein is a novel regulator of the transition from proliferation to differentiation.

The following talks in this session presented data concerning the control of stem cells by material surfaces. Richard Oreffo (Southampton) presented results with mesenchymal stem cells derived from bone marrow. He emphasizes a subpopulation of these cells expressing the STRO-1 for skeletal repair.[3] The biology of cells in vitro as well in vivo for bone augmentation was studied using 3D scaffolds of biomimetic polymers and biomineral-inspired scaffolds with growth factors.[4,5] Carolin Noack (Dresden) demonstrated in a short talk the usefulness of native extracellular matrix produced by SaOS-2 osteoblastic cells or human mesenchymal stem cells as a substrate for bone regeneration. She found that proliferation of mesenchymal stem cells was strongly enhanced on this matrix compared with tissue culture plastic. The experiments also revealed that the quality of the matrix for cell adhesion depends on the age of the cell culture which was used for matrix preparation.

To consider the fact that most tissues including bone require vascularisation to regenerate, James Kirkpatrick (Mainz) demonstrated co-culture experiments of endothelial progenitor cells with osteoblasts on a variety of 3D-biomaterial scaffolds. During these complex cell-material interactions it was found that a network of capillary-like structures developed in the absence of exogenous pro-angiogenic factors.[6] It appears that in this system osteoblasts function as drug-delivery system to drive vasculogenesis. In addition, it was demonstrated that this co-culture on a suitable biomaterial was able to yield microvessel-like structures in an in vivo mouse model.[7]

A short talk by Peter Ciba (Lübeck) demonstrated that pluripotent stem cells from the rat pancreas cultured on a collagen-elastin matrix promoted epithelialisation and vascularisation in a dermal wound. The authors confirmed the survival of the transplanted cells in the tissue, which suggests that the matrix contributes to the epithelial differentiation of the pluripotent cells.

## Bioactivation of Implant Surfaces

Strategies to control cells by tailoring a bioactive material surface involve the modification of physical and chemical characteristics. Molly Stevens (London) presented an overview about the recent developments of biomaterials in her laboratory.[8] The work is focussed on the fabrication of novel nanostructured scaffolds that mimic the nanostructure of the tissues in the body and involves materials for hard and soft tissue engineering.[9,10] For orthopaedic implants, coatings which release strontium were developed. These

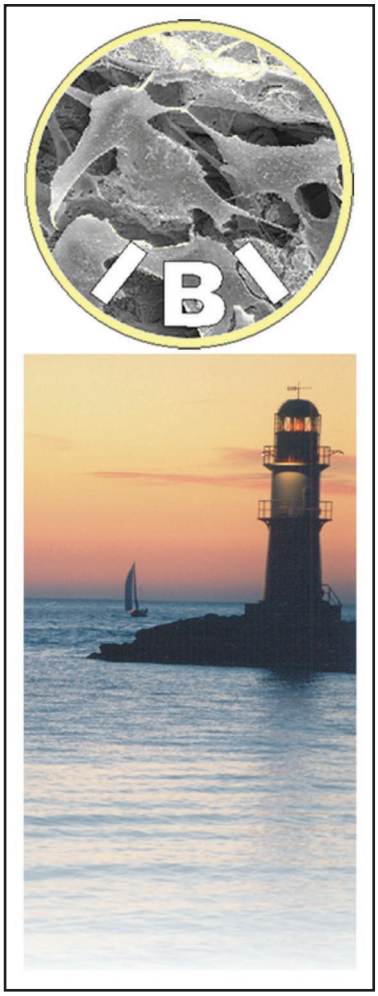


Figure 1. Logo of the symposium "Interface Biology of Implants" (IBI) (Photo by Irma Schmidt, Rostock).

materials are tested concerning the interaction with cells and for bone regeneration in vivo. The talk of Josep Planell (Barcelona) dealt with strategies to bioactivate titanium surfaces and polymers. In his laboratory an elastin-like polymer derived from bacteria was used to be immobilized to the titanium surface by a silane agent. This polymer contains RGD sequences which are binding sites for cellular integrin receptors. The bioactivation of polymers involves the structuring of PMMA and chitosan.[11] PMMA films were patterned using nano-imprinting lithography. The patterns consist of lines in the μm range. This structure was tested concerning the behaviour of neuronal cells. Mathis Riehle (Glasgow) presented fabrication technologies to create polymer surfaces with nanofeatures. A film of poly caprylactone (PCL) was spin cast on a wafer and structured using micro and nanostamps. The final PCL film contained 50 μm high pillars, as well as pores and grooves. To create a third dimension the film was rolled to a tube. Smooth muscle cells were then used to test and optimize the material.

To create bioactive surfaces, Martin Möller (Aachen) demonstrated that to prevent unspecific protein adsorption, hydrogels are coated with star branched polyglycols and polyglycerols that

enable controlled introduction of branching, activation of side chain substitution and specific functionalization.[12] Polyglycerol is a water soluble polymer and can be substituted by a variety of functional side groups. The prepolymers can further be linked to biologically active compounds. By combination of lithographic techniques, copolymer templating and solid-phase synthesis, the concentration, spatial distribution and clustering of bioactive ligands can be precisely controlled ranging from several nanometers up to a few micrometers. Such a model system allows a systematic study of the cellular responses.

Marcus Textor (Zurich) presented techniques which are also aimed to produce surfaces that allow the elimination of unspecific protein adsorption and the addition of bioligands that control the biological response.[13] He used poly(ethylene glycol) and poly(oxazoline)-grafted polyionic copolymers which assemble spontaneously from aqueous solutions at charged surfaces resulting in well defined, immobilized monolayers or multilayers. Two novel surface modification techniques were presented that combine conventional microfabrication with molecular self-organization. Micropatterns of DNA-tagged vesicles are fabricated by recognition and immobilization of the vesicles on a substrate presenting patterns of the complementary DNAs. Using X-ray interference lithography, patterns as small as 50 nm could be produced. Textor further addressed the functionalization of particles for magnetic resonance imaging applications, based on self assembly of functional molecules with biomimetic, catechol-based anchorage groups, derived from mussel adhesive proteins. The catechol-PEG dispersants could also be further functionalized with biotin for conjugation with antibodies aimed at targeted imaging of specific cells or tissues.

In a short talk Sinem Engin from the laboratory of Doris Wedlich (Karlsruhe) presented the interesting idea to immobilize extracellular domains of cadherins as binding partners for cellular cadherins with the aim to drive stem cell renewal or differentiation. For oriented immobilization of cadherins they applied the SNAP-tag technology to link cadherins to surfaces with self-assembled monolayers composed of benzylguanine headgroups containing thiols.

## Adhesion Induced Cell Responses

The interdisciplinary field of the interface between material and the biological system requires a permanent stimulation from basic sciences, notably from cell biology. Mechanisms of cell adhesion, which control signal transduction to induce a biological response in cells play a key role.[14] Cell adhesion involves the dynamic interaction of adhesion receptors with the substrate outside and the actin cytoskeleton inside the cells. Alexander Bershadsky (Rehovot) addressed several new aspects of the feedback signalling mechanisms between cell adhesion and the cytoskeleton.[15,16] He could observe two distinct domains of the lamellar protrusions at the periphery of a migrating cell. These two zones are characterized by different organization of the actin cytoskeleton and focal adhesions. The dynamic interplay with the different components suggests a functional role. Bershadsky further studied the stress fiber formation of the cytoskeleton in dependence on the rigidity of the substrate. Beside differences in the cell shape and organization of the cytoskeleton he found a decreased size of focal adhesions and most strikingly, a lower ability of cells to polarize on a soft substrate. Using a library of siRNAs to suppress the expression of 86 tyrosine kinases, the group of Bershadsky identified 4 genes which are responsible for the blocking of cell polarization on a soft substrate and eight genes which are required for the polarization on rigid surfaces. Thus, these proteins participate in the adhesion-dependent recognition of the substrate rigidity.

To more understand the dynamic molecular mechanisms of focal adhesions, Bernhard Wehrle-Haller (Geneva) presented new concepts for the integrin adhesion and intracellular signalling. He identified two new binding sites in the head domain of the cytoskeletally associated protein talin for β3-integrin which are required for the efficient clustering of integrins.[17] Integrin clustering is facilitated by binding of $PI(4,5)P_2$ to talin which indicates the critical role of the membrane interface. In contrast to the talin-head the talin-rod domain is unable to induce integrin clustering, but is recruited to vinculin and F-actin containing focal adhesion. Thus, talin has two functions in the regulation of cell adhesion.

Further talks demonstrated how these adhesion mechanisms can be controlled by a defined patterning of a material surface. Ada Cavalcanti-Adam (Heidelberg) in close collaboration with Joachim Spatz (Stuttgart) presented data how surface patterning can regulate transmembrane and intracellular protein clustering to mimic both physical and chemical cues of the extracellular space in vivo.[18] Cell spreading and adhesion sites stability depends on the nanometer lateral spacing between single integrin ligands. Initial spreading and focal adhesion formation is inhibited if RGD peptides on the substrate are spaced above a threshold of 73 nm with subsequent consequences concerning the cell shape and adhesion force. Cell polarization and directed migration play a crucial role in many physiological processes including migration of stem cells during tissue repair and regeneration. To apply the concept to immobilize molecular gradients, a modified substrate dip-coating process of block copolymer nanolithography has been developed. Using this technique, a linear increase of the distance between RGD-functionalized gold nanoparticles is achieved at the nanoscale level.[19] The most striking finding was that cells can sense differences in ligand spacing as little as 1 nm along the front and the back of their body, which seems to affect cell polarization and migration.

Andres Garcia (Atlanta) presented data concerning the engineering of artificial materials to direct integrin binding specificity and signalling. These materials regulate in vitro cell function and in vivo healing responses for tissue repair. For example, clinically relevant titanium implants were grafted with a non-fouling oligo(ethylene glycol)-substituted polymer coating and functionalized with controlled densities of the $\alpha_5\beta_1$-integrin specific fibronectin fragment $FNIII_{7\text{-}10}$. This strategy enhanced osteoblastic differentiation of bone marrow stromal cells compared to unmodified titanium and RGD-presenting surfaces.[20] Notably, $FNIII_{7\text{-}10}$ functionalized titanium improved osseointegration compared with RGD-coated and unmodified titanium in vivo. Garcia also demonstrated that generation of multivalent extracellular matrix

ligands, like mixed COL-1/FN ligands enhanced cell adhesion strength and focal adhesion assembly.[21] These surfaces also promoted elevated proliferation rates.

In a short talk Karine Anselme (Mulhouse) addressed the influence of a microstructured surface on the cellular nucleus. When human osteosarcoma cells were cultured on a micostructured surface of a polymer film which presented 4 μm high micropillars with a size of 7 x 7 μm, a deformation of the nuclei of the cells were observed. The nuclei were stretched across the pillars or inserted into the spaces between. Staining of the nuclei confirmed both an altered structure of the chromatin as well as a deformed cell membrane. This is the first observation that topography of the substrate can directly influence the structure of the nucleus, probably mediated by the interaction with the actin cytoskeleton. This finding suggests that the topography can directly control processes of gene regulation in the nuclei.

## Mechanical Control of Cells

There is growing evidence that mechanical forces play a significant role in cell biology and notably during interaction with a material surface.[22] Because of the recent exciting data regarding stem cell control by mechanics,[23] a special session dealt with the mechanical control of cells. Cells are able to sense forces but also actively apply forces to the objects they touch. Dennis Discher (Philadelphia) addressed two topics how cells are able to sense forces via the adhesion system which involves the force-generating myosin motors. By mechanical sensing macrophages are able to decide which are foreign objects to eat them and which are self cells to leave them alone.[24] In a second topic he presented his revolutionizing results that naive mesenchymal stem cells specify lineage and commit to phenotypes with extreme sensitivity to tissue elasticity.[25] Soft matrices that mimic brain tissue appear neurogenic, stiffer matrix that mimic muscle are myogenic and rigid matrices that mimic bone prove osteogenic. Concerning the mechanism he is able to show that inhibition of myosin blocks all elasticity directed lineage specification. Sensing to different rigidities involves structural differences which are attributed to unfolding or dissociation of cellular proteins.[26] In a short talk Tilo Pompe (Dresden) also addressed the role of matrix elasticity and found that site-specific phosphorylation of the signalling protein FAK is controlled by matrix rigidity but not by receptor forces arising from varying ligand anchorage. The mechanical interaction of cells with the matrix in a 3-D collagen fiber network was studied by Ben Fabry (Erlangen). He focused on the traction forces of the cells which are of interest during cell invasion. The results revealed that invasive carcinoma cells generated high strain energy, comparable to highly contractible smooth muscle cells. In addition, invasive cells assumed an elongated spindle-like shape and generated a highly anisotropic strain field which was not observed in non-invasive cells.

One of the most exciting fields in cell sensing of mechanical forces is the switch from mechanical into biochemical signals. The investigations of Viola Vogel (Zurich) significantly contributed to our understanding of the mechanisms, how cells are able to transform mechanical signals into distinct sets of biochemical signals that regulate cellular processes.[27] New tools of nanotechnology and computation begin to reveal how functions can be switched if proteins are mechanically stretched and partially unfolded.[28] In her talk she focussed on the mechanical stretching or unfolding of the fibrillar fibronectin by the cells. Stretching of matrix fibrils will not only increase the rigidity of the fibers but will alter the displayed binding sites. Interestingly, as cells pull on existing fibers and assemble new ones, the old fibronectin fibers differ in their mechanical properties compared with new ones and become increasingly more unfolded with age.[29] Fibrillar fibronectin is also more unfolded on rigid than on soft substrates. We might suggest that these differences in unfolding of fibronectin have physiological significance, because fibronectin has many different recognition sites, e.g., for serum proteins or adhesion receptors. These mechanisms have far reaching implications in tissue engineering, systems biology and medicine.

The dual mechanical interactions of cells with extracellular matrix proteins are mediated by integrins. In a short talk Joachim Rychly (Rostock) demonstrated that a short time mechanical pull on $\beta_1$-integrins without a change in cell shape induced an increased release of vascular endothelial cell growth factor in mesenchymal stem cells prior to a differentiation to an osteogenic phenotype. This indicates that mechanical forces play a role to induce functional activity in undifferentiated stem cells.

Because of the significance of mechanical forces for cellular regulation, physical characteristics of an implant surface are of primary interest. Therefore, Jan de Boer (Twente) established a high-throughput screening system to correlate defined topographies of the substrate with the biological response of the cells. He designed TopoChips consisting of 40,000 variations of topographies in micro- and nano-sizes. Using a special cell seeding device different cell types were cultured on the chips and proteins of interest were fluorescently labelled using antibodies or fluorescent proteins to assess the response of the cells to the various topographies.

## Summary

The symposium is becoming more and more attractive, both for registered participants and internationally renowned invited speakers. This have several reasons, the topic is of increasing relevance for clinical applications, the conference is strongly focused on the interface of medical implants, it brings together the various disciplines and receives input from basic sciences. The symposium has developed to a world-wide leading scientific meeting in this field of research. Therefore, we are looking forward to organizing the fourth symposium, which should be held in 2012 at the attractive location at the Baltic Sea coast.

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