Inducing osteoconductivity

Discussing cell biology and biosystems, **Professor Dr Barbara Nebe**, explains cell-biomaterial interaction involved in geometrically structured implant surfaces and the future of biocomplexity in orthopaedic implants

Could you introduce yourself and how you came to work in the field of biomaterials?

I started in 1980 as a laboratory engineer at the Department of Internal Medicine at the University of Rostock in Germany, concentrating on extracorporeal detoxification, artificial organs and biomaterials. I received my PhD 15 years later, investigating the flow cytometric characterisation of immortalised hepatozytes and the integrin-mediated interactions with the extracellular matrix.

I became assistant professor in 2005 and was then promoted to the role of Professor for Cell Biology at the University. I have since worked to organise and promote a number of international symposia including the German Society of Cell Biology, Interface Biology of Implants and the recent 'Functionalised Bio Materials: Therapeutic Applications' for the European Material Research Society. I have since devoted my career to biomaterials and cell biology, involving interface interactions between materials and biosystems.

What is the objective of your research?

I would like to work with system biologists and computer scientists to find the key players involved in the altered adhesion structures inside the cells, such as the actin filaments. I find this a particularly exciting approach – modelling of cell behaviour right at the interface.

Could you provide an insight into your efforts to investigate the combined effect that topographical and chemical modifications of biomaterial surfaces have on tissue physiology?

The knowledge about cell-biomaterial interaction at the interface of stochastically or geometrically structured implant surfaces is of clinical relevance for an optimised implant ingrowth. The cell behaviour on a biomaterial's surface is highly complex, and we as cell biologists have not fully understood all the adhesion and signalling processes occurring at the interface, until now. Our recent research shows that osteoblasts on a micropillared surface developed an actin pattern adequate to the underlying surface – in mimicry fashion. In interdisciplinary research with engineers, system biologists and mathematicians, we developed a software program called 'FilaQuant', that allows us to quantify these actin filament re-arrangements. We found differences in length and orientation dispersion in actin stress filaments on planar surfaces versus shortened, locally arranged actin fibres on pillars.

How do the chemical features of a biomaterial influence cell behaviour?

In parallel with the topographical influence, the chemical features of a biomaterial are important for cell behaviour on surfaces,

An optimistic outlook for implants

The use of metallic implants in patients is a huge challenge in regenerative medicine. A team of scientists at the **University of Rostock** are designing advanced bioactive materials to tackle this the problem

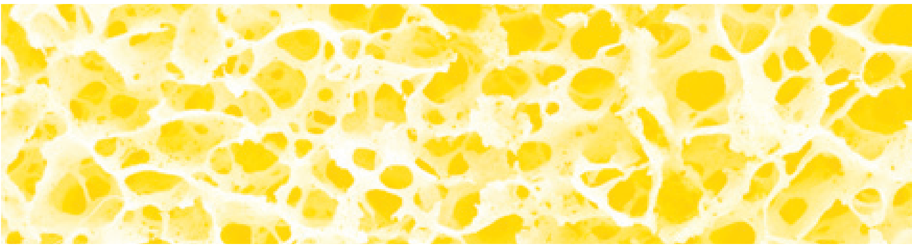
BONE HAS THE remarkable ability to regrow after damage, but to be effective, the process requires either a small fracture space or a facilitating scaffold. Therefore, the practice of orthopaedic surgery – including joint and tooth replacement, fracture healing and reconstruction of skeletal abnormalities – regularly utilises metallic implants during operations. In fact, there are an estimated 4 million operations worldwide involving bone grafting or bone substitutions. Problematically, many of these implants fail due to insufficient adhesion and ingrowth of bone cells to its surface. To control the surrounding tissue and improve the chances of permanent integration, scientists and medical professionals have started to rely on bioactive materials. The ultimate goal for Professor Barbara Nebe at the University of Rostock is to use biomaterials to achieve lifelong secure anchorage of implants in the native surrounding bone. This will prevent an abundance of operations to remove failed implants, saving time and money. Overall, the research she is working on alongside other scientists in her department and across Europe could lead to an improved product for patients while simultaneously improving the state of orthopaedic healthcare.

CHEMISTRY VERSUS TOPOGRAPHY

Effective implants are osteoconductive, meaning they successfully guide reparative growth of the natural bone via bone synthesising cells called osteoblasts. The idea is to control the adhesive interactions of cells with the implant surface. Titanium has been well established as an osteoconductive material due to its biocompatibility, corrosion resistance and excellent mechanical properties. This trait has seized the attention of Nebe's group, which is performing investigations to examine the combined effects of titanium chemistry and topography when it comes to spurring osteoconductive capacity.

Chemical functionalisation involves a variety of materials from metals to synthetic polymers to natural biological materials, while the topography of an implant relates to its surface geometry and roughness. In regard to topography, blasting, etching and oxidation are all techniques that scientists use to achieve surface roughening – an important quality in fostering osteoconductivity in implants. In Nebe's experiments to examine titanium chemistry and topography, she took smooth titanium, gradually increased its microroughness and coated it with plasma polymerised allylamine (PPAAm).

She found success in applying positively charged, nanometre-thin polymer coatings (PPAAm or ethylenediamine) to the implant's surface, as the coatings greatly accelerated the ingrowth of bone cells. The results of her experiment also showed that in all PPAAm modified surfaces, adhesion of osteoblastic cells not only increased



especially plasma polymer layer with positive charges, as they attract cells in their initial adhesion phase. This is due to their negatively charged hyaluronan coat – an extracellular matrix substance released from the cell membrane. A plasma polymer-functionalisation of a metal, such as titanium, is advantageous concerning osteoblastic focal contact formation, as are vinculin, paxillin and p-FAK, and actin cytoskeleton development. Although this layer is only in the nanometre range, cell responses are convincing. For me personally, the question that arose was whether such an adhesive nanolayer could be dominant within the microtopographical cues of a surface.

The initial investigations are surprising, and we discovered cells are no longer able to 'feel' the machined grooves of a titanium surfaces. As a result, cells are able to overcome the restrictions of the surface topography. We are very keen to explore this concept, and indeed this field, in more detail. Furthermore, we learned that cell adhesion in the initial phase can be significantly enhanced by combining topographical and plasma-chemical modification.

Where do you plan to take your future research endeavours?

The main focus for me is to gain further insight into the biocomplexity of cells – especially osteoblasts – at the interface of modified biomaterials. I hope to understand exactly what a cell's response in pattern would be on a geometrically designed surface – what is the 'aim' of the cell in this behaviour?

Likewise, if, for example, the re-arrangement seems to be of a physiological stress response, what preventative action might we be able to undertake in order to avoid the initial response? Moreover, I hope to examine how the requirements of orthopaedics can combine mechanical anchorage of implants and cell/tissue aspects, ie. a fully accepted bioequivalent surface.

significantly in combination with roughness, but they spread across the surface area of the implant and moulded to its shape. "We believe that the combination of topography and chemical modifications results in truly bone-resembling coatings," she states. "Both surface roughness and chemistry must be optimised together to design new biomaterial surfaces and fully explain the phenomena taking place in cell-material interactions."

BACTERIAL INFECTION

A major cause for implant removal can occur due to outside bacteria colonising bone implants, thus leading to infection of the surrounding tissues. Immune response to implants is common, leading to a large proportion requiring replacement. This response can include hypersensitivity to orthopaedic hardware, with up to 13 per cent of people reporting to be sensitive to one or more of the metals nickel, cobalt and chromium. In order to avoid a bacterial colonisation of implants and reduce sensitivity, Nebe has investigated coating them with varying quantities of antibacterial agents such as copper. Together with the Leibniz Institute for Plasma Science and Technology eV (INP) and the Institute of Physics of the University of Greifswald – both located in Greifswald, Germany – the research groups have developed plasma coating processes that are optimal for preventing bacterial attachment.

NEXT STEPS

There is much more still to be discovered regarding cellular reactions at the biomaterial interface, as Nebe explains: "Gaining insights into the complexity of cellular reactions at the biomaterial interface is a huge task for the contemporary research. It is important to recognise changes of the single molecular components of cell adhesion and of the linear signalling pathway of cells at the material interface; however, this will not necessarily lead to insights in the whole cell reaction". To gain these insights, Nebe is focusing her attention on the emerging interdisciplinary field of systems biology, which involves examining interactions between the components of biological systems. This approach will lead her into new waters, as she will combine concepts from bioinformatics and systems science using mathematical models to better understand cell behaviour. Among signalling mechanisms, this will enable her to investigate the relationship between intracellular signalling molecules and the organisation of actin cytoskeleton in osteoblasts. "Our eventual goal is to simulate the cell in silico as it interacts with a given underlying implant surface," she concludes.

INTELLIGENCE

INTERFACE INTERACTIONS BETWEEN BIOMATERIALS AND THE BIOSYSTEM

OBJECTIVES

- To improve the adhesion of bone cells to implants to increase positive outcomes in orthopaedic surgery
- To reduce the number of implants that fail due to bacterial infection

PARTNERS

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BARBARA NEBE began her scientific career at the University of Rostock, where she majored in animal physiology. In 1991, she advanced to the position of Research Associate at the Department of Internal Medicine where she focused on cell biological issues in osteoporosis, interfacial interactions of the biosystem to implant surfaces and regenerative medicine. After completing her Habilitation at the university in 2005, and is now a professor in the Department of Cell Biology.

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