Rapid Prototyping and bioactive processing in regenerative medicine

[*]Freiburger Materialforschungszentrum und Institut für makromolekulare Chemie der Albert-Ludwigs Universität Freiburg

[**]Klinik für Mund-, Kiefer und Gesichtschirurgie, Klinikum der Albert-Ludwigs Universität Freiburg

R. Mülhaupt[*], C. Carvalho[*], R. Landers[*], U. Hübner[**], R. Schmelzeisen[**]

In Tissue Engineering and bone reconstruction, alongside the choice of materials, the scaffold design is of great importance. Three dimensional structures not only permit the tuning of chemical and mechanical properties, but they can also copy the outer form of the required bone or cartilagenous structures. While new processes that create such 3D scaffolds by means of Rapid Prototyping have been developed to allow the use of new bio- and biodegradable materials, they are still restricted to a limited type of materials. At the Freiburger Materialforschungszentrum (FMF) a versatile new process called 3D Bioplotting™ has been developed. Plotting is performed in a zero gravity environment by means of 3D dispensing in liquid plotting media and matching the dnesities of plotting materials and plotting media. A wide variety of plotting materials can be employed including melts, solutions, pastes and reactive monomers, macromonomers and gel precursors. Since processing can be performed at ambient temperature in water also bioactive components are easily implemented into the 3D dispensing process for producing rigid, flexible and also ceramic scaffolds. The scaffold fabrication has been demonstrated for polymer melts (PLLA, PLA, PGA, PCL, PE), pastes of caclciumhydroxapatite and hydrogels (e.g. collagen, agar), as well as two-component systems (e.g. chitosan, fibrinogen, polyurethane). On hard scaffolds, cells are seeded after the plotting process. The biocompatible conditions, used for the fabrication of soft scaffolds, permit the incorporation of cells within the construction process, which makes 3D Bioplotting™ an attractive new RP technique for Organ Printing.Tailor-made biodegradable scaffolds can be fabricated in a short time using individual computer-tomography data from the individual patient. The addition of drugs to the used materials (e.g. growth factors for faster regeneration, antibiotics to prevent infections) is feasible and can be employed also in advanced drug delivery systems. In-vitro tests of scaffolds prepared by means of 3D Bioplotting™ showed promising results and n-vivo experiments are in propgress.

Ultrathin, biocompatible and bioactive coatings for titanium implants

[*]Institut für Technische Chemie, TU Braunschweig

[**]GBF Braunschweig

[***]MH-Hannover

H. Menzel[*], N. Adden[*], A. Hofmann[**], F. Thorey[***], H. Windhagen[***]

Although titanium implant materials are generally considered as biocompatible, a problem still exists in the osseointegration of Ti orthopedic implants. Small gaps between the implant and the bone are open to particles or bacteria, which leads to a chronic inflammatory response followed by mechanical failure of the implant [1]. One way to improve the integration of the implant into the bone is to encourage a fast bone growth to the implant surface by coating the titanium with a biocompatible and bioactive thin polymer film. An approach to such films is to find a polymer which improves the biocompatibility of the titanium implants and to find a way to incorporate bioactive substances like the protein BMP-2 [2]. This approach includes two mayor challenges. The first is in finding suitable polymers. Because no correlation has been established between the physicochemical characteristics of a material and the reaction of the body towards the material, a screening of different polymers is necessary.

Recently, phosphonic acid molecules were used for SAM formation on titanium and higher hydrolytic stability compared to silane SAMs [3] and that no surface conditioning is required. For the screening of 22 different polymers the “photochemical grafting onto” method basing on silane chemistry [4] was expanded to titanium surfaces employing phosphonic acid groups [5].

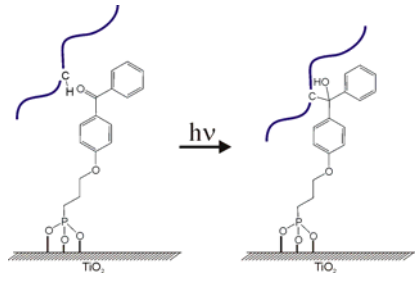

figure 1: photochemical grafting to titanium surfaces

The different polymer surfaces were screened for their compatibility with osteoblasts. As expected the cells grew differently on the different polymer surfaces. The correlation between the contact angle values of the surfaces and the cell growth was examined, but no clear conclusion could be drawn. However some candidates showing good biocompatibility in the in-vitro experiments have been identified. These results have been verified in first in-vivo.

Furthermore, we investigated the possibility to bind proteins to activated monolayers of hydroxyundecyl phosphonic acid and carboxyundecyl phosphonic acid on titanium. X-ray photoelectron spectroscopy (XPS) and time of flight secondary ion mass spectroscopy (Tof-SIMS) were used to characterize the chemistry and structure of the different surface modification steps. Binding of model substances and BMP-2 to these surfaces was confirmed. In-vitro and in-vivo experiments are under way.

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Multifunctional Implant Materials

GKSS Research Centre Geesthacht, Institute of Polymer Research, Teltow

A. Lendlein

Most polymers used in medical applications today are materials that have been developed originally for application areas other than biomedicine. Each application requires a specific combination of material properties (e.g. mechanical properties) and biomaterial functionalities. With the increasing number of potential applications the realizable number of property- and functionality combinations increases. A substantial development in this context is the introduction of polymer systems in which macroscopic properties can be tailored over a wide range for a specific application, and which can be functionalized according to the demands of application. Biofunctionality, hydrolytic degradability, and shape-memory functionality are examples for functionalities. An actual trend in polymer science is the design of materials which show multifunctionality meaning an unexpected combination of material functionalizations. Degradable implants for minimally invasive surgery or active scaffold structures as temporary substitute of the complex natural extracellular matrix are examples for applications of such multifunctional materials.

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Nanostructured Biomaterials

[*]Institute for Inorganic Chemistry of the University of Hanover

[**]German Research Centre for Biotechnology

[***]Department of Otorhinolaryngology at the Medical University of Hanover

P. Behrens[*], P.P. Mueller[**], Th. Lenarz[***], M. Stieve[***], I. Krueger[*], H. Mojallal[***], N. Witteck[***], B. Süß[***], B. Borisov[***], S. Diste[***], C. Turck[***], F. Dimpfel[***]

Although it has been known for a long time that topographical features of a surface with micrometer dimensions can influence cell behaviour, the influence of nanometer-sized structures has only recently been explored. It could be shown that the nanotopography of a material has a decisive influence on cell adhesion, cell growth, cell proliferation and also on cell differentiation. Whereas basic studies on cells placed on nanostructured materials can yield important insights into the mechanisms of cell behaviour on the nanoscale, nanostructures can also be used to optimize the function of implants. Nanostructured biomaterials can be constructed in several ways, using physical techniques (as lithography, two-photon polymerization or laser structuring) or chemical methods. Apart from using preformed polymeric or inorganic nanoparticles which are then immersed in a binder, more sophisticated chemical methods rely on the direct formation of nanostructured materials, for example by precipitation of a solid from a solution. Such processes can be controlled by the addition of organic molecules and then yield organic-inorganic hybrid and composite structures which, by the removal of the organic phase, can be transferred to nanoporous solids. Nanostructures can be present only on the surface of a material or throughout its bulk, in the latter case allowing for adaptation of the size and the shape of an implant during the implantation procedure without compromising the nanostructure. Nanoporous materials in addition allow for the delivery of drugs and biomacromolecules.

The aim of our work is the generation of a material for improved middle-ear implants for the reconstruction of the ossicular chain. This problem is special when compared to other regions of the human body where implants are used. A specific task of a middle-ear prosthesis is the conduction of sound from the drum to the inner ear. In the middle ear, the implant is not immersed in a body fluid, but is surrounded by air. Whereas in the case of other bone implants, a fast and strong ingrowth of natural bone is usually required (i.e. a biomaterial with a high bioactivity is needed), excessive bone formation would compromise

the sound transmission of a middle-ear implant, defining the quest for a biomaterial with adapted bioactivity. Whereas commonly used metallic middle-ear implants obviously differ strongly from bone in their chemical make-up, structure and properties, nanostructured organic-inorganic materials at least partly resemble the natural material. Also, nanostructures should help to control the bioactivity of potential biomaterials for middle-ear implants.

The research was conducted within the work package D1 of the SFB 599 as a collaboration between the Institut für Anorganische Chemie of the Universität Hannover, the Gesellschaft für Biotechnologische Forschung in Braunschweig, and the Hals-Nasen-Ohren-Klinik of the Medizinische Hochschule Hannover.

Neuro-stimulation in Neuro-Rehabilitation

Center for Sensory-Motor Interaction, Department of Health Science and Technology, Aalborg University, Denmark

T. Sinkjær

An injury to the central nervous system can result in a permanent loss of the voluntary motor function and sensation. However, the peripheral motor and sensory nerves below the level of lesion often remain intact, and so do the muscles. Functional Electrical Stimulation (FES) is a technique to restore motor and sensory functions after such injuries. The forces generated in muscles activated by FES can be graded by varying the stimulus pulses, but the relationship of the force to the stimulus pulse varies in a complex manner that depends on, for example, muscle length, electrode-nerve coupling, and activation history. Several studies have shown that the application of closed-loop control techniques can improve the regulation of the muscle activation. Natural sensors such as those found in the skin, muscles, tendons, and joints present an attractive alternative to artificial sensors for FES purposes because they are present throughout the body and contain information useful for feedback control. Moreover, the peripheral sensory apparatus is still viable after brain and spinal cord injuries. Electrical signals can be recorded using long-term implanted nerve cuff electrodes in the human peripheral nerves. Reliable detection of sensory nerve signals is essential if such signals are to be of use in sensory-based functional electrical stimulation neural prosthetics as a replacement for artificial sensors (switches, strain gauges, etc.). In this lecture the signal characteristics of the sensors, the nerve interface, signal processing, and example of human applications to restore motor functions are described.

In the second part of this presentation, stimulation of sensory nerves in CNS injured persons to improve their motor functions through neurorehabilitation will be addressed. Neurorehabilitation is a term that relates to methods and technologies for maximising the functioning of impaired sensory-motor mechanisms in human after central nervous system (CNS) injury (e.g., spinal cord injury and stroke). Maximising function relates to developing new sensory-motor pathways and CNS strategies that could benefit from the available sensory-motor mechanisms. This presentation focuses on functional electrical therapy (FET) to promote recovery. The FET comprises two elements: 1) electrically induced activation of both afferent and efferent neuronal pathways on impaired extremities by a neural prosthesis device and 2) repetitive exercise of paralysed extremities.

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Biotribology of Artificial Hip Joints

Institute of Medical and Biological Engineering, School of Mechanical Engineering, University of Leeds

Z. Jin, E. Ingham, J. Fisher

Natural synovial joints such as hips and knees are remarkable bearings. These bearings are expected to function in the human body for a lifetime whilst transmitting large dynamic loads and yet accommodating a wide range of movements. However, diseases such as osteoarthritis, rheumatoid arthritis and trauma sometimes require these natural bearings to be replaced by artificial ones. Total joint replacement has been the most successful surgical treatment for hip joint diseases in the last forty years. Currently, about 1 million hip joint replacements are carried out every year world-wide. The majority of these devices utilise a material combination of ultra high molecular weight polyethylene (UHMWPE) articulating against either a metallic or ceramic component, and can sometimes last 20 years in the body without failure. However, osteolysis and loosening of the prosthesis has been recently identified as the main factor limiting the in-vivo performance of implants, particularly with the increasing use of these devices in younger patients with life expectancies after surgery in excess of 25 years. The osteolysis and loosening are usually caused by an adverse tissue reaction to wear particles of UHMWPE. Other forms of bearing couples have been extensively introduced recently to reduce wear and wear particle generation, such as cross-linked UHMWPE-on-metal or ceramic, metal-on-metal, ceramic-on-ceramic and metal-on-ceramic.

Importance of tribology in artificial hip joint replacements will be reviewed, from studies of friction, wear and lubrication. Particular focus will be on the use of different bearing surfaces such as metal-on-metal and ceramic-on-ceramic as well as different forms such as resurfacing.

Machining of Ceramic Functional Surfaces for Complex Prostheses

Institute of Production Engineering and Machine Tools, University of Hanover

B. Denkena, M. Reichstein, M. van der Meer

In Hannover the Collaborative Research Centre “Biomedical Engineering” was brought into being, whereby engineering technology, natural sciences as well as medical science and cytology interdigitate. One central subject concerning the permanent implants is the development of automated working on the free form surface of low-wear ceramic implants, which is promoted under medical and technical points of view with the aim of optimized lifetime. This theme will be presented with a close relation to production engineering.

Over longer periods of use conventional implants consisting of metal and plastic components face problems like implant loosening and immune reactions. The main reason for the failure of the interconnection between bone and prosthesis is the agglomeration of wear debris of the polyethylene part [1]. Besides strong pain functional losses are resulting consequences and a revision operation becomes necessary. In particular knee implants have a short life span. More than 90% of the patients need an operation to replace the implant already after 10-15 years [2]. Encouraged by the successfully employed ceramic hip joint prostheses a trend for the development of implant material pairings goes towards the use of wear reducing ceramic on ceramic combinations. The complex kinematics and geometries of the knee joint, have so far prevented their widespread use in total knee arthroplasty. In the first place high-precision machining processes for free formed surfaces have to be developed. Secondly ceramics cannot cope with non-uniform loads, which implicates a new design for the complex shaped prostheses adjusted to the material properties. Nevertheless on the whole favourable are the lower friction coefficient, the more than 200-times smaller wear debris and the increased bio compatibleness of ceramics [3].

The technologies in development for five-axis grinding and polishing will enable the fabrication of variegated kinds of complex prostheses for medical technology. The known superiority of hip joint replacements will be made accessible for patients, which are in need of complex shaped implants, for example knee joint prostheses. The interrelation of the machining and the generated work piece properties concerning surface and subsurface quality as well as form accuracy will be illustrated.

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Future Cochlear Implant electrode

Department of Otolaryngology, Medical University Hanover

T. Lenarz

Auditory rehabilitation of deaf patients with cochlear implants has proven to be very successful. They provide an open speech understanding to the majority of patients under quiet conditions. However the speech understanding in noise is markedly reduced. This can be related to the limited information transfer at the electrode nerve interface. Compared to a normal hearing cochlear the number of information channels is substantially compressed in a ratio of 1:1000. To overcome these present limitations several experimental approaches are investigated at present. Their common goal is to increase the number of separate information channels.

1. Improved mechanical properties of electrodes with a close proximity to auditory nerve neuron. This approach is followed by preformed electrodes, which move towards the medial wall of cochlear after insertion. Experimental electrodes are also inserted into the modiolus or direct nerve contact.

2. The regrowth of spiral ganglion cell dendrites using neurotrophins is the first step of a specific nerve material contact.

3. Specific surface modifications in the micro- and nanometer scale will specifically influence the adhesion of spiral ganglion cells onto electrically stimulating contacts.

4. Functionalized electrode surfaces using specific cell adhesive molecules will allow the specific ongrowth of spiral ganglion cell dendrites onto the stimulating substrate.

5. The manufacturing of thin film electrodes on a solid state substrate will allow to produce electrodes with a much higher number of electrode contact which will be the basis for a sufficient number of information channels.

6. Specifically programmed stem cells which are attached extracorporally onto the electrode substrate will help to contact the spiral ganglion cells specifically on a cell-to-cell interaction and can be used also for central auditory prostheses.

The increased number of electrically separated electrode channels will allow to use more advanced signal processing strategies for information coding closely to the natural hearing process.

Polymers for Drug and Gene Delivery to Cells an Tissues

Dept. Chemistry and Pharmacy, University of Regensburg

A. Göpferich

Besides the pharmacological profile of a drug substance, additional factors such as its stability in biological media, or its distribution in the body are important parameters that determine its therapeutic value. Over the last decades we have learned that adjuvants which can be used for drug delivery can contribute substantially to drug efficacy. Especially problematic substances such as proteins and peptides frequently require such ‘packaging materials’ to achieve a sufficient level of effectiveness in a therapy. DNA and RNA are another example for substances that need to be processed together with supplementary adjuvants. Both types of molecules alone frequently fail to achieve sufficient cellular uptake due to their polyaninonic character, leading to a significant handicap for crossing biological barriers such as cellular membranes.

Polymers are a class of materials that can help substantially to overcome some of the outlined limitations [1]. They can be used to ‘encapsulate’ sensitive drugs to increase their in vivo half life. Concomitantly they can be used to control drug pharmacokinetics by regulating drug release by mechanisms such as diffusion, erosion or swelling. In addition, polycationic materials can be used to complex DNA to form so-called polyplexes, which are potent nucleic acid carriers allowing for substantially facilitated transfer of DNA to tissues and cells. Despite this progress, contemporary research efforts towards the design of better polymer materials still thrive. In recent years especially the polymer surface design came into the focus of this development.

It is widely accepted that interactions between materials and cells or tissue are always related to interactions of the living system with a material surface. For protein and peptide drugs, the attachment to polymer surfaces seems to offer significant advantages over the classical incorporation into the bulk followed by release thereof. Surface tailored biomimetic materials [2] signal to cells with precise resolution in space and time so that eliciting biological responses with high precision seems to be possible. Further progress has been made towards the development of new polycationic carries. Strategies are being developed to de-couple their outstanding ability to shuttle DNA in to cells from their substantial toxic potential.

The talk will focus on developments in the field of biomimetic materials and polycationic materials for the delivery of DNA. Aspect such as polymer material surface design, and polymer degradability are promising new tools that seem to have a major impact on providing solutions to problems related to regenerative medicine and gene delivery applications.

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Molecular approaches to biocompatibility

Department of Gene Regulation and Differentiation, GBF, Gesellschaft f. Biotechnologische Forschung mbH, Braunschweig

H. Hauser

Biocompatibility is a prerequisite for the implementation of new implants.It includes the acceptance and function of an implant after interaction with the periimplantation tissue. In order to ensure this, in vitro and in vivo test systems have been established ranging from in vitro cultures of cells with the materials to preclinical animal models. For in vitro test systems classical read-out parameters are viability, proliferation and differentiation. In animal model studies mostly histopathology and overall parameters are monitored. Often, the evaluations from different test systems do not lead to the same conclusion. This is partially due to the fact that complex systems do not only reflect direct and indirect effects but also the three-dimensional and mechanical conditions of implants in an organism. While the complex models are more informative for real life applications it is difficult to separate primary events from follow-up reactions. A systematic development of new materials and surfaces would, however, need information about such initial signals and events induced by the implant. Further, the use of animal models is restricted by ethical considerations and by the costs, such that extensive screening is preferably done in vitro and only a limited number of pre-selected materials are to be tested in vivo. A major goal in biocompatibility research is therefore the detailed understanding of primary events, in best case on the molecular level. The second goal is to analyse the pathways by which primary events lead to the complex phenotype seen in animal models and in patients.

Studies on the molecular level have been greatly stimulated through knowledge and technological developments in genomics and proteomics in the last decade. The available technology yields very detailed information from very small samples. Further, bioinformatic tools enable the integration of the resulting data with existing knowledge and thus to transform pure analytical data to functional understanding. Today, the global analysis of cellular events are studied on the level of proteins and nucleic acids. The chemical nature of nucleic acids has allowed to advance technologies in way that a certain automatisation is possible and high-throughput analysis is possible. Although protein analysis is more informative the level of complexity is orders of magnitude higher and the current capabilities are still limiting.

The implementation of molecular analysis in current biocompatibility test systems is hampered by the genomic diversity of the species that are currently used. To overcome this problem the close interaction of the different disciplines is required.

In the presentation these issues will be highlighted by examples from ongoing work in the SFB599 and future opportunities will be discussed.

Biomimetic approach to composite biomaterials

AGH –Faculty of Materials Science and Ceramics, Department of Biomaterials, University of Science and Technology Krakow, POLAND

J. Chłopek

One of the impulses in development of biomaterials is connected with the materials mimicking the constitution of organic systems. These systems created by nature are characterized by structures and processes which permit them to perform their functions in an optimum way. To biomimetic structures we can count graded, grained, laminated and fibrous structures.

In this work it has been showed the various types of composites with carbon and polymer matrices. Depending on the matrix type and sort of modifying phase (fibers, particles) it is possible to obtain implants with controlled mechanical properties, bioactivity and degradation time. The mechanical and biological properties and durability of the composites were analyzed under “in vitro” an “in vivo” conditions. These composites can be applied as implants, scaffolds for tissue regeneration and as external stabilizers, in which mechanical signal is used as bone tissue growth stimulator. The modifying additives change not only mechanical properties but also they have influence on resorption time of polymers. Performed tests allowed to elaborate of implants in the form of plates, screws, nails etc. with controlled mechanical and biological properties mainly for bone surgery.

CT Investigations: Mechanical and Structural Properties of Magnesium Sponges

Institute of Materials Science, University of Hanover

D. Bormann, Fr.-W. Bach, R. Kucharski

Within the presentation investigations of magnesium sponges with a micro computertomograph will be presented.

The first part of the presentation acts about the production of magnesium sponges and the application of the microCT for quality assurance.

The structure of magnesium sponges e.g. thickness of plateau borders and pore diameter are calculated.

Compression tests have been carried out to investigate the collapse of sponges. The results are used to verify the Finite Elemente Simulations.

Bone as a Hierarchical Material - Osteoporosis Treatment and Biomimetic Replacement Materials

[*]Max Planck Institute of Colloids and Interfaces, Department of Biomaterials, Potsdam, Germany

[**]Ludwig Boltzmann Institute of Osteology, Vienna, Austria

[***]Materials Physics Department, University of Vienna, Austria

P. Fratzl[*], H. S. Gupta[*], W. Wagermaier[*], M. Inderchand[*], A. Woesz[*], M. Rumpler[*], P. Roschger[**], K. Klaushofer[**] , H. Peterlik[***]

Bone is a hierarchically structured material composed of collagen and mineral [1]. Bone fracture is dependent on the architecture and composition of bone on all hierarchical levels and is dramatically influenced by the local orientation of the collagen fibrils [2] as well as by their interaction at the nanoscale [3]. In particular, the propagation of cracks in bone is dramatically hindered by the complex lamellar architecture of the material [2]. As a consequence, when evaluating the efficiency of osteoporosis treatments in preventing fractures, it is essential to consider the effect of the treatment on bone mass together with possible alterations of bone material quality [1]. Known effects on bone quality in treatments with bisphosphonates or fluoride will be discussed.

Moreover, biomimetic design of bone replacement materials suggests a hierarchical organisation of scaffolds with porosity on several length scales [4, 5] and with an organic-inorganic composite structure [5, 6]. Such highly porous structures with controlled internal architecture can be fabricated by rapid prototyping techniques, both in ceramics [4] or in ceramic-reinforced biopolymers [5]. Continuous internal pores with diameters in the range of a few tenths of mm allow bone-forming cells to proliferate throughout the scaffold [4, 5] and the free-form fabrication allows a tuning of mechanical properties at constant porosity and density [7].

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From Bench to Bedside: Rationale for Implant Surface Modifications in Arthroplasty

Department of Orthopedics, Annastift, Medical University of Hanover

H. Windhagen

Successful endoprosthetic implant fixation is a prerequisite for the long-term survival in arthroplasty. Developments of micro-porous titanium surfaces and calcium-phosphate layers have improved the bone-implant interface substantially and lead to long-term survival of implants (10 year over 95%) such as primary hip stems. However, these principles of surface modifications do not exhibit similar results in situations with small surface area and high shear forces, such as the acetabular cup, knee and shoulder-glenoid prostheses. Furthermore, implant-bone gap bridging in revisions or implant-bone anchoring in inflammatory situations as rheumatoid arthritis or bone necrosis is still not satisfactory. Thus, despite improvements there is a high demand for improving implant surfaces, especially with respect to the aging population as well as the younger population with high expectations towards joint function, mobility and athletic activity.

Understanding all aspects of the microenvironment around total joint prostheses (TJA) is the basis for design and development of endoprosthetic surface modifications. This microenvironment includes several biologic and biomechanical aspects: Metallic atoms from corrosion act as haptens inducing immune responses and enhance osteolysis. Implant materials are different from bone in terms of elastic modulus and stiffness, causing stress shielding in combination with poor implant design. Surgical injury and micro motion induce fibrous tissue in the interface, where type-B lining cells promote solid-to-solid lubrication but may loosen the implant. Pumping action of cyclically loaded joints produce synovial fluid pressure waves dissecting the bone-implant interface. Cyclic loading and instability lead to mechanical and ischemic reperfusion injury, particle formation, third body wear and osteolysis. This osteolysis is based on foreign body inflammations which on their part interfere with physiologic bone regeneration by blocking the intracellular signalling process of stem cell differentiation and activation.

Advanced designs of implant surfaces have to address this microenvironment by the process of implant bio-activation. Signalling molecules at the implant surface alter the pathologic microenvironment with anti-inflammatory, bone inductive and angiogenetic actions. Such molecules with widely known action and interferences are the Bone Morphogenic Proteins (BMP) which in a broader sense are skeletal proteins involved in bone repair during physiologic bone reparation. The inductive action of these proteins could previously be demonstrated on several indications related to bone healing. Recent research in

collaboration with the SFB 599 has addressed the potential of binding these proteins via surface polymers to titanium by the development of activated self assembled monolayers.

The complexity of the implant-bone interface makes predictions of clinical success in surface modifications complicated. Because in-vitro cultures address only few micro-environmental actions of modified materials, implant survival can only be tested in animal models. Even more complicated are species-related signalling cascades which can only be addressed in clinical studies. The scientific community therefore has to address precise and non-invasive monitoring tools that measure implant migration in clinical situations. The goal of these techniques is to identify implant migration already after several months instead after a decade when implant loosening becomes clinically obvious. Recent research has addressed these problems by advancing the method of radiostereometric analysis (RSA) in collaboration with the SFB 599.

Electrophysiological Assessment of the Inferior Colliculus as a Site for an Auditory Prosthesis

Department of Biomedical Engineering and Kresge Hearing Research Institute, University of Michigan, Ann Arbor, MI

H.H. Lim ,D.J. Anderson

The success and limitations of cochlear implants (CIs) along with recent advancements in deep brain stimulation and neural engineering have motivated the development of a central auditory prosthesis. Current efforts have focused on the auditory brainstem implant (ABI). However, there is a need for a new implantation site due to the lack of success of the ABI, particularly for neurofibromatosis type II patients, and the existence of deaf patients who cannot benefit from CIs. A potential site is the inferior colliculus central nucleus (ICC) (Lim and Anderson, 2003). The ICC is a highly organized tonotopic structure and is more surgically accessible than the cochlear nucleus in humans (Lenarz et al., ARO MWM 2004).

To assess the potential for an auditory midbrain implant (AMI), we stimulated different regions along the frequency and isofrequency dimensions of the ICC and recorded the corresponding neural activity along the tonotopic gradient and across different layers of the primary auditory cortex (A1) in guinea pigs using multi-site Michigan probes. The stimulus consisted of single, monopolar electrical pulses (200 μs/phase, negative leading phase). Current source density analysis, acoustic-driven response patterns, and histological techniques were used to identify the location of each site.

Overall, ICC stimulation achieved lower thresholds, greater dynamic ranges, and more localized, frequency-specific activation in A1 than cochlear stimulation (cochlear data taken from Bierer and Middlebrooks, 2002). However, we observed that location of stimulation within an isofrequency lamina of the ICC affected these A1 responses. Stimulation of more rostral ICC regions elicited larger evoked potentials, greater activation spread (along the tonotopic gradient), more temporally diffuse responses, and lower thresholds of activation in A1. In fact, stimulation of some caudal ICC regions did not elicit any A1 activity (even at our maximum level of 56 μA), which may be indicative of greater inhibitory interactions and/or differences in functional projections compared to more rostral regions.

These results suggest that ICC stimulation may enhance both frequency and level discrimination with reduced energy requirements compared to cochlear stimulation. Furthermore, location of stimulation within the ICC may affect performance. Stimulation of more rostral ICC regions may achieve lower perceptual thresholds but with a cost of greater frequency channel overlap and possibly less precision in temporal coding. The lack of

activation via caudal ICC stimulation suggests the possible need for more complex stimulation strategies that may require a three-dimensional electrode array.

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In vivo und in vitro Verschleißmechanismen in künstlichen Hart/Hart-Paarungen für Hüftgelenke

Universität Duisburg-Essen, Werkstofftechnik II, Duisburg

A. Fischer

Seitdem Endoprothesen in der Hüftchirurgie eingesetzt werden, konnte die Lebensdauer durch stete Forschung und Entwicklung verlängert werden. Dies wurde durch verbesserte klinische Operationstechniken, angepasste Designs and verbesserte Werkstoffe erreicht. Unter normalen Umständen erreichen 95 bis 97% aller Hüftendoprothesen eine Lebensdauer von mindestens 10 Jahren. Natürlich wären Lebensdauern von 20 Jahren und mehr wünschenswert. Um dies zu erreichen müssen u.a. die folgenden Fragen beantwortet werden:

Mit welchen Mechanismen stören Partikel welcher Größe, Form, Oberfläche und chemischen Zusammensetzung die biologische Umgebung?

Wie können wir systemseitig die Anzahl der freigesetzten Partikel vermindern?

Dieser Beitrag befasst sich mit der Tribologie künstlicher Hart/Hart-Paarungen auf der Basis von Laborversuchen und von klinischen Erkenntnissen. Aufgrund der Tatsache, dass alle Partikel in der Nähe der Oberfläche durch die Entstehung und Ausbreitung von Schädigungsmechanismen erzeugt werden, ist zunächst eine Analyse des tribologischen Systems durchzuführen. Daran schließt sich die Bestimmung der wirkenden Hauptverschleißmechanismen und deren Untermechanismen an. Diese beschreiben die physikalischen und chemischen Prozesse, die für die Partikelentstehung charakteristisch sind, und stellen somit eine direkte Verbindung zwischen den Eigenschaften und dem tribologischen Verhalten der Werkstoffe dar.

Bis heute sind künstliche Hüftgelenkspaarungen in Bezug auf klinische Studien und Laborsimulationen gut untersucht. Leider verzichtet man dabei vielfach auf eine Bestimmung der aktiven Verschleißmechanismen. Aus diesem Grund wird versucht ein Überblick über den Stand der Forschung zu geben, der auf der Basis des Zusammenhanges zwischen Werkstoffen, Tribosystem und wirkenden Mechanismen vorhanden ist. Im Wesentlichen werden die Besonderheiten vorgestellt, die zur den tribosystemabhängigen Mechanismen der Erzeugung und Ablösung von Verschleißpartikeln führen. Auf der Grundlage dieser Zusammenhänge werden neue Entwicklungen im Bereich von Beschichtung und Randschichtbeeinflussung vorgestellt.

Stichworte: Hüftgelenksprothesen – Verschleiß – Schmierung – Verschleißmechanismen – Tribochemische Reaktionen – Oberflächenzerrüttung

An Approach Towards Kinematics in Total Joint Replacement: the in vitro Experimental Investigation

Laboratory for Biomechanics and Biomaterials, Orthopaedic Department, Hanover Medical School

C. Hurschler

In the age of rapid advancements in the areas of computer simulation, motion analysis, and imaging techniques among others, in vitro experimental methods nonetheless remain an indispensable tool in the area of musculoskeletal biomechanics. Already as early as in the latter half of the 1900th century, it was recognized that no one approach to investigating the biomechanics of the human body or its joints alone would suffice, and that in vivo investigations, mathematical models as well as in vitro experimental and functional anatomical investigations are necessary in order to investigate important questions regarding the function of the human joints. Although the palette of methods available to the researcher today is vastly superior to those available in the past, this basic principle still applies.

This presentation will provide a short historical overview of the experimental methods that have in used in the field of joint mechanics, and how newer technologies available today have advanced the quality of the in vitro simulations that can be performed. Electromyography has enabled the relative activity of muscles to be measured which has improved the incorporation of active muscle forces in experimental simulations. New technologies, optical, magnetic, as well as ultrasound, have enabled the precise measurement of the motion of bones and implants during the simulation of physiological and or pathological conditions. And finally, industrial robots in combination with six-axis load cells have opened new horizons for the investigator.

The Laboratory for Biomechanics and Biomaterials (LBB) possesses unique joint-kinematic simulators that have been used to investigate clinically relevant research questions in the areas of knee total joint arthroplasty (TKA), high tibial osteotomy and the function of the infrapatellar fat pad. The use of a sensor-guided industrial robot for the investigations of the biomechanics of the shoulder will also be presented. This device has been used to investigate the effect of prosthesis geometry on the kinematics and kinetics of total shoulder arthroplasty (TSA), operative techniques for improving shoulder stability and the repair of the shoulder socket, as well as basic research questions regarding the role of the intraarticular vacuum in controlling shoulder socket joint motion.

To illustrate the principles involved in these simulations, selected studies of the function of shoulder and knee prostheses will be presented. This context will further serve to illustrate

how the knowledge gained from such simulations can be used to provide valuable information for the clinician implanting such devices. Another aspect of importance that will be illustrated is the verification of the function of existing and proposed new devices, which is an important topic for the SFB 599. Such a functional analysis provides important information which can also lead to and improvements in the design of current devices as well as help the clinician decide which device is best suited to deal with a particular clinical situations or patient groups.

KFO 102 Biomechanics and Biology of Bone Healing

Charité – University Medicine Berlin, Center for Musculoskeletal Surgery

G. N. Duda, N. P. Haas

A thorough understanding of musculo-skeletal loading, biological processes of initial and late phases of bone healing and the genetic basis shall help to accelerate a successful patient's healing and rehabilitation free of complication. To do so, an understanding of biology and mechanics throughout the process of bone healing is mandatory. Multiple factors indicate a close relationship between healing outcomes and mechanical conditions. Till now, no direct conclusion may be drawn from the initial mechanical stiffness of an osteosynthesis on the biological reaction during healing and the final clinical outcome. For surgeons, the small size but large number of fragments is especially demanding to achieve an accurate repositioning of meta- and epiphyseal joints. The reduced bone quality, especially in elderly patients and the complex anatomical situation in these regions further increases the efforts necessary to achieve satisfactory results. Especially for complex fractures of the epi- and metaphysis an optimization of the mechanical conditions could allow additional support for the biological healing process. To achieve this, the Clinical Research Group combines basic research in the field of biology of healing and biomechanics with clinically established image analysis and modern planning and navigation tools.

Applications of Implants in Small Animal Medicine and Outlook on Future Possibilities

Small Animal Clinic, University of Veterinary Medicine Hannover, Foundation, Germany

A. Meyer-Lindenberg, C. Hackenbroich, I. Nolte

Introduction

Veterinary medicine has gone through many changes in the past decades. While in the beginning, diagnosis and therapy of diseases of farm animals where the main concern, treatment of domestic animals, especially dogs and cats, has become the main focus. Parallel to the development in human medicine, the demands pet owners have of veterinarians have grown. This has lead to the expansion of diagnostic and therapeutic procedures, which have been increasingly established in veterinary medicine. As part of this, various implants for bone and soft tissue surgery were introduced into veterinary medicine. In the following, the most important of these will be described as examples for different indications.

Implants in soft tissue surgery

Stents

Permanent stents (dilatable wire mesh) made of various non-absorbable materials (e.g. titan-nickel-alloys) are used in veterinary medicine to treat tracheal collaps, which is often seen in the small toy breeds. In tracheal collaps part of or the complete trachea down to the bronchi can be affected. Clinically, tracheal collaps is mainly associated with dyspnoea, which greatly affects the quality of life of the canine patient. Implantation of a stent can stabilize the collapsed area and the function of the trachea is reestablished.

Coils and Ameroid constrictors

In veterinary medicine, coils are implanted for treatment of different vascular malformations as e.g. a persistent Ductus Arteriosus Botalli or an intrahepatic shunt and lead to occlusion of the affected vessel through local thrombosis. These permanent implants are applied through a catheter, which is inserted into the vascular system under fluoroscopy. Compared to conventional methods, this procedure is less invasive.

The Ameroid constrictor is a ring-shaped, incompletely closed implant, which is also used in vascular surgery. It is used especially for treatment of extrahepatic shunts. The Ameroid

constrictor is placed around the shunt vessel, which needs to be closed, and maceration of the core of the constrictor leads to occlusion of the blood vessel.

Cardiac pacemaker

Also in veterinary medicine cardiac pacemakers are implanted. However, this procedure is generally only performed in specialised clincs. The most important indication for the implantation of a cardiac pacemaker in a dog or cat are syncopes as a result of bradycardias, which are caused e.g. by AV-blocks or the "sick sinus sydrome".

Intraocular lenses

Intraocular lenses are now routinely used to treat cataracts in dogs and cats. They are made of various materials as e.g. polymethylmethacrylate (PMMA) or acryl. After extracapsular phacoemulsification, they are implanted into the remaining lens capsule. The lens has a diameter of ca. 7mm and requires a much higher number of diopters compared to humans (40- 42 dpt). The anchoring is achieved with the aid of haptics of different lengths depending on the size of the animal.

Implants in bone surgery

Plates, screws, wires, pins, interlocking nails etc.

These implants made of medical steel or titanium are the largest group of implants in veterinary medicine and are used for osteosyntheses after fractures or for correctional osteotomies. Due to the different sizes of the animals (cat, small and large dogs, e.g. Great Dane) a wide range of implants is needed. Of plates and screws sizes from 1.5mm to 4.5mm are used and different types of plates (neutralisation plate, dynamic compression plates (DCP), Limited-Contact-DCP (LC-DCP), No-Contact-DCP etc.) are available.

Most implants remain in the body for a limited time and are removed after healing of the bone. Many of the implants applied in veterinary medicine are available from human medicine, but there are also especially developed implants for veterinary indications, such as acetabulum plates or 2.0 mm DC-plates for fracture repair of long bones in small patients.

The surgical techniques, instruments and implant materials conform to the standard of the work group for osteosynthesis (Arbeitsgemeinschaft für Osteosynthese, AO), which has a specialty group for veterinary medicine (AO-Vet) affiliated to the human medical AO.

Prostheses

In veterinary medicine, endoprotheses are routinely implanted into large-breed dogs for treatment of hip dysplasia (HD). In smaller dogs with hip problems, resection arthroplasty gives good clinical results. In most commercially available protheses developed especially for veterinary medicine, the acetabular cup consists of polyethylene (PE) and the head and shaft

are made of medical steel or titanium. Depending on the system used, they can be implanted with or without using cement.

In diseases of other large joints, as e.g. ellbow or stifle, artificial joint replacement has not been established yet.

Outlook on future possibilities

In addition to the routine use of implants, veterinarians are cooperating with medical doctors and material researchers of the university in different projects. One example is the SFB 599.

One aim of this collaborative research center in the partial project R6 is the development of resorbable implants based on magnesium alloys for stable fracture repair of load-bearing bones in animals and humans. Such resorbable implants would have several advantages for the patients. Not only the associated anesthetic and surgical risk of a second surgery for implant removal but also the high costs of this second procedure are eliminated. Because of the lower E-modulus of the magnesium alloys, which is similar to that of bone, and also due to the controllable corrosion, stress protection as can be seen with rigid titanium and especially steel implants can be prevented. Furthermore, the implant can be adapted to the fracture and degradation can be controlled to occur at the same rate as the healing of the fracture.

Another focus of research are prosthesis, especially total hip replacement, which are investigated in the projects D5 and D6 in the SFB 599. Tribiologic tests as well as computer-aided simulations of implantation of hip prostheses are aimed at increasing the endurance and reducing the number of revisional operations.