Solved and unsolved Material Aspects in Spine Surgery

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INTRODUCTION: Spinal diseases cause very often pain and disorders. Several treatment options consider conservative or operative treatment. High percentages of the cases result in residual pain and reduced function. Principle goal of all treatment is the re-establishment of daily activity, the increase of quality of life and the shorten of time back to work. Since clinical success is not certain, the medical doctor shall consider alternative treatment strategies as well. Implants and instruments shall consider the "2nd line of defence".

METHODS: Goal of surgical treatment is the re-establishment of spinal biomechanics with its alignment and mobile function adequately. It must be acknowledged that no implant is able to stop the degeneration process of the spine and its segments. Implants are able to compensate mal-functions or provide additional stability to the bony structure.

Major steps in launching new developments:

- Understand the pathology and the clinical problem
- Understand the biomechanical shortcomings of the disease
- What biomechanical solution can solve the problem?
    - Implants
    - Surgical technique
    - Instruments
    - Approaches

Design of implants and instruments have a significant influence on the success of the treatment; however, there are other factors to be considered like diagnosis or rehabilitation. Pain experience is the major reason to see a medical doctor. Pain is a subjective indication with different impact for individuals.

Implants shall provide adequate stability depending on the treatment strategy:

- Stiffness to achieve bony fusion as well as static and dynamic strength
- Low friction and durability for motion preservation devices
- Elasticity and dampening properties in order to reduce load sharing
- Quick bone attachment on the implant surface, including primary and secondary fixation

In the meantime, instruments shall ease the implant insertion and placement as well as eventual repositioning. Reduction of incision size is essential in order to minimize post-operative pain.

RESULTS: Exemplary developments where several materials are considered:

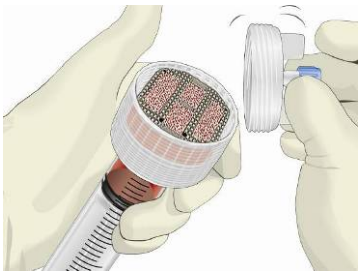

Fig. 1: Interbody fusion device provided with perfusion kit (SynCage-LR$^{chronOS™}$)

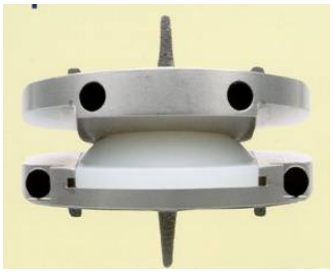

Fig. 2: Total Disc Replacement implant (Prodisc) containing articulating components and means for primary and secondary fixation to bone.

Fig. 3: Cervical fixation plate comprising translational and polyaxial features.

DISCUSSION & CONCLUSIONS: Clinical success of operative treatment of spinal diseases might be evaluated after long term postoperatively. Today's activities may address more sophisticated diagnosis and biomechanical understanding. New technologies are necessary in order to address new clinical requirements.

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Wear Testing of Implants – State of the Art

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INTRODUCTION: Wear testing of implants, initially being developed by single research labs, has become a worldwide standard procedure for research and development. Whereas the performance and complexity of new wear simulator techniques becomes more and more sophisticated, the clinicians' acceptance of laboratory results is still limited. In-vivo failure of simulator tested devices might have contributed to the current gap between fact and fiction.

HIP WEAR TESTING: Hip simulators are standardized by ISO 14242-1 and ISO 14242-3. Simulator wear rates of standard couplings such as metal on UHMWPE meet the data provided by long term clinical studies [1]. Despite initial problems such as negative wear rates published for new crosslinked polyethylene materials (XPE), more recent studies meet the XPE clinical wear data [2,3]. Nevertheless, important wear mechanisms such as subluxation of ceramic on ceramic bearings, impingement and fatigue fracture of XPE materials have not been predicted.

Wear particle analysis is one of the standard accompanying test procedures. Whereas the assessment of particle size and shape has become routine for most labs, the focus on nano size particles is new and suggests that we might have underestimated the osteolytic potential of wear debris in the past [4]. At the same time, the impact of motion types on the particle generation is investigated leading to the fact that standard walking cycles as required by the normative references might not replicate the particle distribution seen in the patient [5].

KNEE WEAR TESTING: Due to the complex type of load and motion, wear testing of knee implants becomes even more challenging than wear testing of hip implants. Two different types of simulators used worldwide are trying to replicate the in-vivo situation: The so called "deflection controlled" type is standardized by ISO 14243-3 describing the motions of the implant. In contrast, ISO 14243-1 is focussed on the loads ("load control") acting on a knee implant. Whereas the first test method is easier to realize by a knee simulator, the second one is more flexible in investigating different types of knee implants (e.g. semi-constrained types). Recently, an ongoing discussion about the stiffness of the knee soft tissue has lead to an update of the current ISO 14243-1 becoming available within the near future. As seen for hip implants, the clinical failure mechanisms of knee implants such as failure of tibial posts [6] are not fully reproduced. The lack of daily living activities such as rising from a chair or stair climbing are assumed to contribute to this discrepancy.

SPINAL DISC WEAR TESTING: The development of recent spinal disc implants has been accompanied by the wear test standard ISO 18192-1. This standard is based on very little knowledge available on the daily living motions. Nevertheless, the clinical wear rates have been well reproduced [7,8]. As seen for hip and knee implants, failure mechanisms such as impingement have become clinical relevant. Again, this type of failure is not reproduced by standard testing.

Fig. 1: EndoLab® ISO 14243-1 knee simulator.

CONCLUSION: Future developments in simulator testing will have to incorporate complex types of motions as well as non standard loading conditions seen in patients. Regardless the capability of a test frame, experience is required to address all potential failure mechanisms.

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Solved and unsolved problems in surface treatments and functionalization of implants

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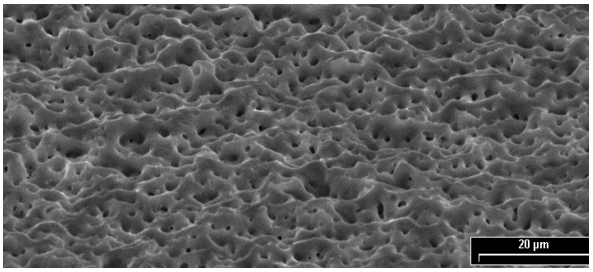
INTRODUCTION: The evolution of the surface treatment of implants follows the evolution of the definition of biocompatibility, a term which has been introduced 50 years ago. Starting from biological inert surfaces it has been adapted to biological active and finally to functionalized surfaces. In order to improve the tissue integration and subsequently the long-term maintenance, the implant surface can be modified by mechanical, physical, chemical or biological functionalization. Chemical and electrochemical surface treatments are well suited to modify the surface topography, the surface energy and to control the chemical composition of the outmost layer which plays a relevant role on the biological performance of the material. Chemical and electrochemical industrial surface treatments of titanium implants include: passivation, etching, colour anodisation, alkaline anodisation, electropolishing and glow discharge anodisation.

Passivation occurs in an oxidizing solution like nitric acid and provides a controlled and uniformly oxidized surface consisting in a dense and stable TiO_2 film two to six nanometers thick, improving the corrosion resistance (decreases ion release). The passivation procedure eliminates metallic contaminants from the surface without affecting the overall surface topography of titanium surfaces. **Etching** is applied prior to anodisation in order to decontaminate the surface and to enhance the coloration density. An etched surface doesn't need to be passivated before anodisation. Etching can be applied as a final treatment. It increases roughness and supplies a mechanical functionalization**. Colour anodisation** is the formation of an oxide film of TiO_2 with a thickness in the range of 30 to 300 nanometers, proportional to the applied voltage. The oxide film acts as an interferential filter leading to beautiful colours in the same sequence as the rainbow when the voltage is increased. **The alkaline anodisation** also consists of a TiO_2-layer but with a higher thickness of about three micrometers. The coating is characterized by a grey colour, anti-galling properties and wear resistance as well as increased fatigue strength of 15% to 20% as compared to uncoated parts. The coating is uniformly distributed and tends to level off surface imperfections. **Electropolishing** provides the titanium parts with a clear and shiny appearance and removes impurities resulting from the machining. Usual ablations are in the range of 2 to 10 µm, allowing an initial roughness of 0.7 µm ($R_{a)}$ to decrease down to 0.2 µm. Electropolishing is also well suited to deburr parts by dissolving sharp edges preferentially. It also increases fatigue strength by levelling out crack initiations and avoiding hydrogen embrittlement. The **glow discharge anodisation** occurs under high voltage with sparks formation. The resulting TiO_2-layer is 5 to 10 µm thick and incorporates calcium and phosphorous elements in significant amounts. The coating is characterised by a rough and porous structure which is bioactive.



Morphology of a glow discharge anodisation layer BIOCER® containing Phosphate and calcium components (SEM picture)

Biofunctionalization can be achieved by two different approaches, (i) the Drug Delivery System or (ii) the grafting of bioactive compounds. The latter is more appropriate on anodisation coatings. An example is given with a glow discharge anodisation grafted with phosphocreatin molecules.

If the mechanical, physical and chemical surface properties can be satisfactorily measured, the evaluation of the biological response of living tissues and biological fluids on the different surfaces is much more complex and represents a strong limitation in the development and application of bioengineered surfaces. This field requires a stronger multidisciplinary understanding between material scientists, biologists and clinicians.

Implant Coatings as a Means of Delivering Pharmaceuticals

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INTRODUCTION: The idea of an implant coating that promotes bone quality improvement whilst at the same time does not irrevocably attach the implant to the bone is a challenge for designers of orthopaedic implant coatings. There are many Orthopaedic procedures, for example CMF and Traumatology, in which a key user need is that implantable devices fixed with screws, may be subsequently removed. The need to remove screws may arise for a variety of reasons: it may be that the patient requests it, or that some postoperative complication arises such as loosening or migration, or even that the surgeon is reimbursed for the removal surgery.

THE CLINICAL PROBLEM: We estimate (based on share of the fixation market) that the worldwide usage of bone screws exceeds 100 million. This makes the humble bone screw the most commonly implanted device. Screw loosening in bone is reported to be in the range 3[1] – 6.5[2] % percent. In a particular class of screws "hip screws" the migration is called "cut-out". In an elderly patient such an event may result in death due to complications of a second surgery to fix the problem.

STRATEGIES TO CHANGE BONE: If bone quality in the region of a screw could be improved then logically any failures as a result of inadequate bone quality might be reduced. One means to achieve this is to deliver an antiporotic drug, eg bisphosphonates, parathyroid hormone, and strontium ranelate through an implant coating. Local delivery is attractive as it may reduce or even eliminate the complications associated with systemic drug use. A good example is bisphosphonates. The high affinity of bisphosphonates to calcium means that they will not migrate more than 0.5 mm into the bone surrounding the implant. Local delivery of bisphosphonates was proposed by Wermelin et al[3]. In their technique a bisphosphonate is delivered through a nanolayer of deactivated fibrinogen coating a screw. They observed a gradual increase with time of the pullout force to remove the screws that were treated with the bisphosphonate. Interestingly such a coating does not greatly increase the removal torque thus making it an excellent candidate for use with screws.

HUMAN APPLICATION: It is a significant step to extrapolate the improvement in bone quality around screws in rats to the same occurring in humans. A device that worked in this way would be a considered a combination drug/device and the regulatory path would have to demonstrate that the combination was both safe and effective in controlling implant migration in-vivo. This is possible using Roentgen Stereophotogrammetry (RSA) in which the motion of different segments of bone and implant may be tracked in 3 dimensions. Tantalum beads added to a screw and to the adjacent bone will allow very accurate tracking of the screw migration relative to the bone. Uniquely for orthopaedic clinical trials it is possible to conduct such a study as prospective, double blinded randomized. This will enable a very accurate assessment of screw migration through bone and quantitative assessment of the effect of the drug.
The study design for an evaluation of lag screw cut-out in hip fracture patients is presented.

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[3] K. Wermelin, P. Tengvall and P. Aspenberg (2007) Surface-bound bisphosphonates enhance screw fixation in rats – increasing effect up to 8 weeks after insertion. *Acta Orthopaedica* **78**:385-92

Innovative Production Technology 3D Laser Material Ablation

Microstructuring and Creation of Geometries in Medical Implants

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INTRODUCTION: Three dimensional laser material ablation (Laserengraving) has been commercially used for 10 years. Target was the production of small cavities for the plastic injection industries. Another field of this innovative technology was the production of tribology surfaces and structuring of parts. Continuous development of this technology and better beam qualities of new laser sources, make it possible, to produce finer and smaller structures. Due to the possibility to machine ultra hard materials as well as such which are not conductible, new fields for the production of microstructure medical implants are opened.

MACHINE TECHNOLOGY: The configuration of a laser engraving machine is partitioned in three main components. The first component is the laser source [1], the second component is the scanner unit with the optical components [2], the third one is the machine frame with the mechanical z-axis. Optional x- and y-axis for positioning the machining parts / materials are available.

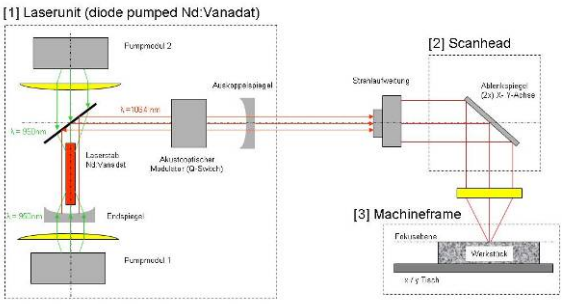

Fig. 1: Laserengraving machine with detailed beam source

The used laser sources (power, pulselength, wavelength) are different and are a function of the machined material and the dimension of the generated structure or geometry. The output power of used laser sources in the micro laser ablation process is not higher than 20 W. The pulselength varies in the range of ns down to ps. Three different wavelengths are in use: 1064 nm for small geometries, 532 nm and 355 nm for smallest machining tasks. The precision of the scanhead and z-axis are very important for a high accuracy of the machined dimensions.

Requirements for the machine frame are a good mechanical stability and a very high thermal drift stability. During machining processes no dynamic forces are available, which is a great advantage.

PROCESS: Laser material ablation (laser-engraving) is a thermal process. The laserbeam is absorbed by the material which is heated, melted and finally evaporated. The vapour is sucking into a filter device.

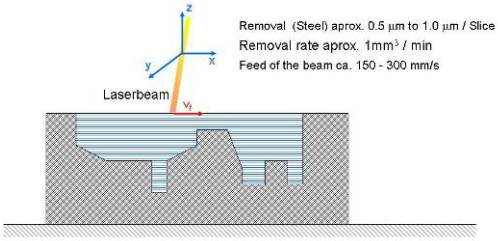

Fig. 2: Schema of laser ablation process

x- and y- dimension of the geometry is generated by the scanhead (2 moving mirrors), z- dimension by moving the z-axis. The control of the beam movement is based on a 3D-CAD created STL-File.

DISCUSSION & CONCLUSIONS This new technology opens new uses in the area of medical implants.

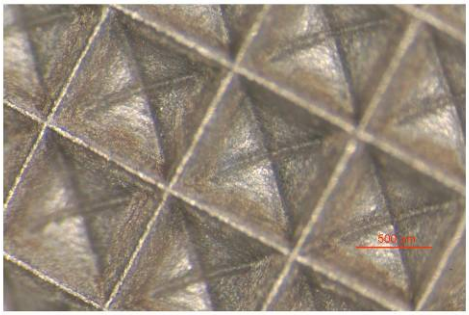

Fig. 3 Example of a technical structure produced with laserengraving

Encountered challenges like unsatisfactory precision, great area structuring (segment) and flash free machining are being explored. We are confident to solve the above-mentioned problems in the near future.

Analysis and Surface Modification of Rapid Prototyped Titanium Structures

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INTRODUCTION: The aim of Rapid Prototyping (RP) technologies is the production of parts directly out of CAD data within a short time and without the use of any tools or cutting devices. These generic processes allow the manufacturing of extremely complex structures with almost no restriction in freedom of design [1]. The material properties, however, cannot be compared with the manufacturing accuracy, mechanical properties and surface structure achieved by conventional abrasive processes. Therefore, the study of the microstructure and mechanical properties of such new materials produced by a new technique is crucial. Furthermore, the biocompatibility of implants strongly depends on the surface chemistry and topography.

METHODS: Selective Laser Melting (SLM) is used as a powerful Rapid Prototype method. Metal powder is locally molten by a scanned continuous wave Ytterbium fibre laser that traces layer-by-layer until the final structure is built. Assembled parts are then heat-treated and characterized by their microstructure, density and mechanical properties. The topography of rapid prototyped titanium surfaces is further modified by sandblasting, shot-peening, vibratory deburring, spark anodisation, electropolishing, etching or anodisation. Scanning electron microscope analysis is used to study the influence of the rapid prototype process parameters to the microstructure and to the surface morphology.

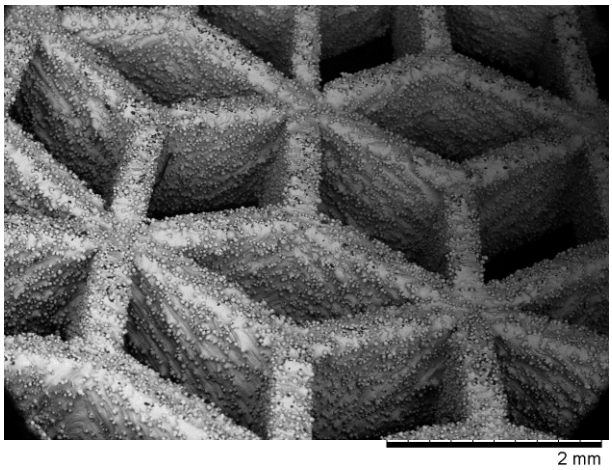

Fig. 1: Native SLM structure.

RESULTS: It is possible to use complex shaped CAD models or anatomic data from CT or µCT sources and to transform them directly into metallic structures with micro-features and virtually 100% material density. Depending on the given process parameters, terminating faces of the building layer are rough due to sintered spherical titanium particles that were not fully fused into the solid body, see figure 1. Directly after the SLM laser process, Ti-6Al-4V structures show a lamellar α / β duplex structure with low ductility. Heat treatment, however, significantly alters the microstructure (see figure 2) and the mechanic material properties.

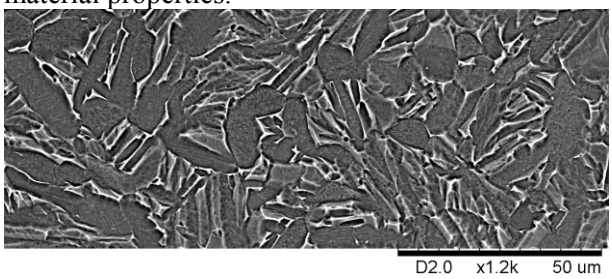

Fig. 2: Microstructure of generatively fabricated Ti-6Al-4V sample after recrystallization anneal treatment at 925°C for 4 hours in inert gas atmosphere.

DISCUSSION & CONCLUSIONS: Rapid prototyped Ti-6Al-4V structures produced by Selective Laser Melting show a particular microstructure which influences further surface modifications. There is a significant difference in mechanical properties between generatively and conventionally processed materials. The performance can be enhanced with carefully selected thermal post-processing in an inert gas atmosphere.

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Orthopedic Implants with Integrated, Designed Network Structures for Improved Osseointegration

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INTRODUCTION: An implant that does not provide long-term fixation and needs to be replaced prematurely causes unnecessary trauma for the patient, and it is therefore vital to reduce the risk of this occurring to a minimum.

One of the major "Fit and Forget" factors for orthopedic implants is the implant's ability to attach itself to the hosting bone.

The conventional methods to improve bone ingrowth by adding a porous coating of titanium beads or hydroxyapatite to the implant's surface work well, but still do not provide the optimum conditions for osseointegration.

PROJECT: Adler Ortho Group, the Italian manufacturer of orthopedic implants, had been investigating alternative means to promote bone ingrowth for some time when it was introduced to Arcam's Electron Beam Melting (EBM) technology, and realized how it can be used to build orthopedic implants with integrated network structures that are conducive to bone ingrowth.

The EBM technology manufactures parts by melting thin layers of metal powder. The energy source is an electron beam and the process takes place in a vacuum chamber, making it well suited to manufacture parts in reactive materials such as titanium. Its additive, layer-based nature also enables the production of implants with the integrated porous surfaces that enhance the osseointegration.

Adler Ortho therefore decided to develop a completely new acetabular cup, able to take advantage of the full range of possibilities that the EBM technology offers. The material of choice was Ti6Al4V with its combination of strength and excellent biocompatibility.

The first project step was to decide on the design of the acetabular cup's network structure. The chosen design was a structure with inter-spaces of 700 µm (Fig. 1) throughout the outer surface.

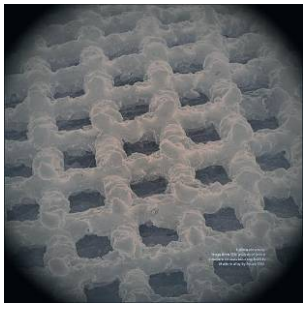

Fig. 1: Network structure

This dimension enables the bony trabeculae to bring about excellent grafting, favoring the ingrowth of new bony tissue.

Fig. 2 (taken two weeks after surgery) illustrates spongy bone observed in the repair phase with thin and dense trabeculae surrounding the implant, penetrating into the space created by the network's macro-porosity. The bone is directly attached to the metal without any fiber tissue interposition.

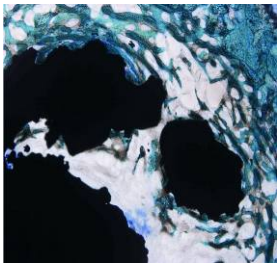

Fig. 2: Spongy bone and implant

Following the clinical and biomedical trials, the process to certify the new Fixa Ti-Por acetabular cup in accordance with the European regulations for medical implants was initiated, covering also the EBM production process and the Arcam-supplied materials, and Adler Ortho was awarded the CE certification in January 2007.

The CE certificate was the final part of the group's product puzzle, and in July 2007 the new, ground-breaking acetabular cup (Fig. 3) was launched as a commercial product.

Fig. 3: Fixa Ti-Por acetabular cup

RESULTS: Since its introduction on the market more than 1.000 cups have been implanted in several Italian reference centers. The surgeons' post-op feedback is excellent: the primary fixation granted by the hemispherical press-fit is supported by the strong surface grip of the cup design.

A post market clinical follow-up has also been put in place to fully evaluate the medium and long-term results of the product.

The Fixa Ti-Por cup is now in series production at Adler Ortho, and its engineers have also started to investigate other new, innovative implant designs to be produced with Rapid Manufacturing.

Product-Mismatch – What is Permitted?

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INTRODUCTION: In the last couple of years, hip surgery has become extremely popular. Not only do elderly people want to stay mobile as long as possible, but also hospital directors have discovered the profitability of the orthopaedic surgery. Due to the considerable number of cases and the above-mentioned increase of interest of various parties, the hip market has become highly competitive nowadays. About 300 different hip implants, which are promoted by a multitude of distributors, can be found on the European Market. Owing to the availability of a vast number of different hip implants and respective components the combination of components from different manufacturers seems to be very customary, e.g. the cup or the inlay of company X will be mixed with the femur head of company Y.

Fig. 1: Different components of a hip implant.

DEFINITION: Typically total knee or hip implants are delivered as so-called product systems or units, each consisting of different CE-labelled components. The product information sheet usually excludes the manufacturer's liability in case of a combination with external products. Thus, a person disassembling an existing, conform system and mixing it with (incompatible) external elements, be it – in case of a hip-implant - the cup, the inlay, the head or the cone, actually commits a **product-mismatch**.

RESULTS: While reassembling the components into another system the surgeon turns into a **manufacturer** of an in-house produced medical device. Article 19[3] of the Medical Devices Ordinance (MepV) says: "*Whosoever changes medical devices or (...), or has them changed or (...), in such a manner that they no longer serve the intended purpose or provide the intended performance, must meet the requirements for the first placing on the market.*" The existing medical device system, which has been tested for its configuration and was approved by a declaration of conformity is, therefore, modified. With the replacement or substitution of an incompatible component, the declaration of conformity of the original manufacturer **expires**. Hence, the person carrying out such a product-mismatch needs to comply with all the regulations being set up for manufacturers, such as the instructions for product surveillance, vigilance, maintenance, … As long as the person complies with these rules, there will not be any restriction against a product-mismatch based on *public law*.

DISCUSSION: Artificial hip joints are complex systems, and the success of a Total Hip Arthroplasty depends on many factors. However, based on *civil law*, the surgeon risks being grossly negligent and therefore sueable civilly. Such is being affirmed in case of violation of established medical therapy rules or trusted medical knowledge. In hip surgery the composition of the different parts and their biomechanical behaviour is crucial for a qualification as gross negligence.

The mixing of *hard* (ceramic/metal) heads with *soft* (polyethylene) external cups or inlays (hard-soft tribological pairing) is widely common and – as a matter of fact – accepted by most manufacturers. But the same combination with *hard/hard* components can have catastrophic consequences for the patient and therefore was consequently assumed as a gross negligence. A mismatch of *hard/hard* components may only be without legal consequences in case of an explicit permission in the product information sheet and reciprocal release from the manufacturers, the International Standards Organization ISO or the FDA.

CONCLUSIONS: The present standards do not allow combining components of different manufacturers unless explicitly stated in the product information sheet or being approved by manufacturers, the ISO or the FDA. As the exact composition of a specific implant is not always obvious, a surgeon should only pair components which are clearly intended to be paired. The product information sheet does contain this information. The safe philosophy is clear: Never mix and match or else, ask the manufacturer in uncertain situations.

Focused Ion Beam Technology for the Evaluation of Material Interfaces

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INTRODUCTION: The success of an osseo-integrated implant depends on both, its capacity to interact with cellular events during early wound healing and its long-term stability provided by a high implant-to-bone contact. Several techniques are available which describe the interface between implant, cells and tissues as stained ground sections for light microscopy (LM), scanning electron microscopy (SE and backscatter mode), transmission electron microscopy (TEM) and microcomputed tomography (μCT).

No single of these preparation techniques is completely devoid of artifacts. Mechanical force during LM preparation can result in gap formation at the interface. TEM analysis of the interface requires either electropolishing or separation of the tissues from the implant which may result in disruption of the interface.

Focused Ion Beam (FIB) technology is an established method to produce cross sections of all kind of materials and their combination. A beam of high energy Ga^+ - Ions is milling the substrate away opening the view with the electron beam of the SEM into the depth. By polishing the cross section, artefact free images of layers, materials errors, inclusions etc. can be made. The advantages of the FIB technology in implants interfaces with organic tissue is the lack of any mechanical stress compared to conventional polishing, leading to a real image of the material intersection.

MATERIALS AND METHODS: Dental and orthopedic implants of various manufacturers surgically removed from humans were used to evaluate interactions between organic tissues and the implant surfaces. They have been investigated by various techniques as LM, SEM, TEM, μCT and FIB[1-3].

RESULTS: In addition to the well described possibilities of other evaluation techniques, the FIB provided SEM surface and cross-section analyses (Fig. 1) as well as 3D SEM tomography of the tissue-implant interface. The FIB technology also allowed for TEM specimen preparation by creating 2 SEM sections back-to-back to each other, leaving an electron transparent lamella for TEM evaluation (Fig. 2).

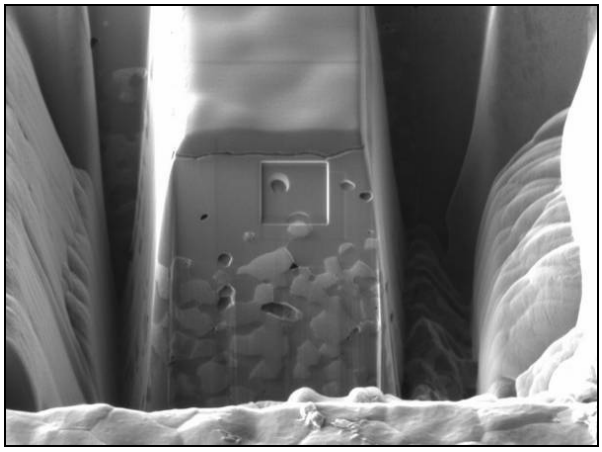

Fig. 1: Cross-section SEM analysis of deep structures as provided by FIB technology.

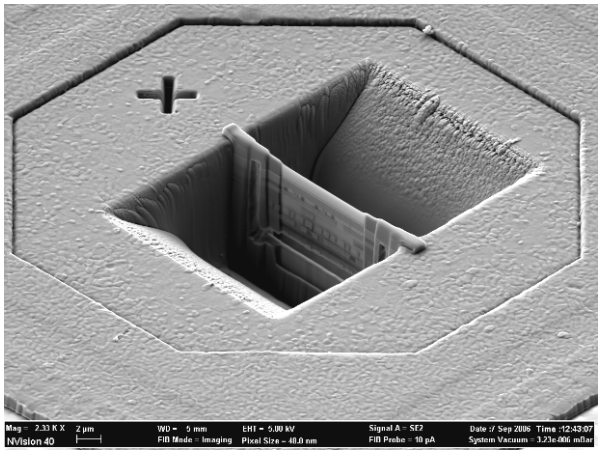

Fig. 2: Transparent lamella milled free by FIB technology from the bulk sample to be investigated by transmission electron microscopy.

DISCUSSION AND CONCLUSIONS:
The FIB technology offers excellent possibilities for the evaluation of material interfaces at a high resolution.

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Osteointegrative Surfaces for CF/PEEK Implants

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INTRODUCTION: Implants made out of carbon fibre reinforced poly(ether ether ketone) (PEEK; > 50% endless carbon fibres) have proven excellent performance in orthopaedics and trauma applications. Their mechanical properties are similar to the ones of e.g. titanium grade 4, especially strength and fatigue properties. Generally, icotec's CF/PEEK implants have a lower modulus, leading to lower stress shielding at implant/bone interfaces compared to metal implants.

The biocompatibility of the material has been proven in numerous studies. Usually, tissues do not adhere to the inert and smooth surfaces, making the material perfect for trauma applications. However, in certain cases (long term implantation), tissue and especially bone ongrowth may be desired. For this purpose, we have developed titanium plasma spray coating (VPS Ti or APS Ti), applying thin layers of pure titanium to the implants. The coatings were mechanically and chemically investigated. Coated screws were tested in a sheep model to study their in-vivo performance, bone ongrowth and removal torque.

METHODS: Vacuum plasma spray coating (VPS) of titanium powder was applied to standardized >50% CF/PEEK (>50% vol/vol CF) specimens for testing of tensile and shear adhesive strength of the layer. Adhesive strength was measured according to ASTM F1147 (tension) and ASTM F1044 (shear). Chemical analysis was done by x-ray photoelectron spectroscopy (XPS) at AlKα irradiation (15kV, 15mA).

VPS coated screws were implanted into diaphyseal cortical bone of Swiss Alpine Sheep. Removal torque after 3 and 6 months was measured and compared to the values of uncoated screws. Histological analysis was done to investigate the bone/implant interface.

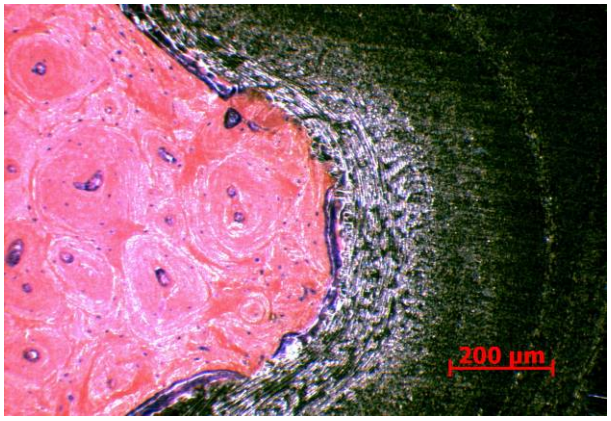
RESULTS: Tensile and shear strength values of the layers applied with VPS and APS are displayed in table 1. Average layer thickness was 70 µm.

Table 1. Tensile and shear adhesive strength of VPS Ti layers on CF/PEEK.

	Tension / MPa ASTM F1147	Shear / MPa ASTM F1044
VPS	22.2 ± 1.3	29.7 ± 6.5

XPS showed that the surface layer consisted of TiO_2.

Removal torque of the screws was significantly greater at both time points, 3 and 6 months ($P<0.001$). Histological analysis showed significantly less soft tissue around coated samples as compared to the uncoated ones but much more direct bone integration and contact. The figure below shows a Giemsa-Eosin stained section through a single thread of a coated screw. There is direct contact of new bone to the Ti-layer and the implant (light shining fibers).



DISCUSSION & CONCLUSIONS: The herein described studies have been part of mechanical and biological investigation of VPS Ti coating on icotec's CF/PEEK implants. From these studies, it can be concluded that VPS titanium coating may be an excellent treatment for CF/PEEK long term implants to promote bone ongrowth. Next steps may be the development of hydroxyapatite coatings on CF/PEEK. This would enable us to provide osteointegrative metal-free implants, featuring artefact free imaging.

ACKNOWLEDGEMENTS: AO Research Institute is acknowledged for conduction and evaluation of the in vivo study.

Antimicrobial Implant Coatings

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INTRODUCTION: Modern medicine continuously develops new artificial short-term or permanent devices to assist in the performance of physiological functions. Implantation of medical devices represents one of the most important risk factors of all nosocomial infections, when implant materials become infected due to bacterial adhesion and subsequent formation of biofilms. The latter are impossible to treat with antibiotics and represent a dramatic complication for the patient, leading to implant replacement, in the worst case to death. Therefore, prevention of bacterial adhesion and biofilm formation is important.

METHODS: We have developed new coordination compounds with silver ions and specially designed ligands. This way, one can tune the structure, the light stability and, most importantly for the biological application, the solubility. With an appropriate chemical linker, one is able to connect such compounds to metallic surfaces forming a nano-structured coating. We have investigated this coating using several methods, namely powder x-ray, XPS, AFM, SEM, micro- and nano-calorimetry and antimicrobial studies with different bacteria as well as biocompatibility studies with fibroblast cells.

RESULTS: XPS and powder x-ray analyses have shown that we deposited the compound [Ag(L)NO3], described previously[1]. The AFM revealed peak-like structures. The surface pattern corresponds to Ostwald ripening motifs on a two-dimensional surface with a main interpeak distance of 20-30 nm, a distance which is known to be ideal for cell ongrowth[2]. The coating can be estimated to be roughly 0.0125g/m^2. The solubility was shown to be very low. Antimicrobial tests were carried out. In a reservoir, a single bacterial strain, *S. sanguinis*, suspended in sterilized human saliva, was added. Treated samples, and non-treated blanks, were exposed during 60 min to a flow rate of the bacteria saliva suspension similar to physiological oral conditions. The vitality of adhered bacteria was evaluated by applying a dual fluorescent staining, with the result that 99% of bacteria were killed.[3] Plating of coated samples in Agar in presence of *S. epidermis* or *S. aureus* for 24h showed the formation of large inhibition zones of the order of >2 cm. The antimicrobial properties were confirmed by microcalorimetry, measuring the bacterial cell multiplication heat. Cell viability was verified on fibroblast cells for the given concentrations.

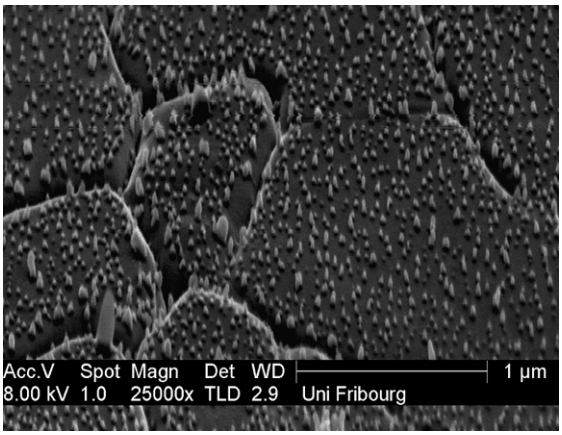

Fig. 1: Nanostructured coating of [Ag(L)NO$_3$] on the surface of Au(111).

DISCUSSION & CONCLUSIONS: Our compound was shown to form regular material coatings on different metal substrates. Furthermore the antimicrobial properties are proven for dental as well as general implant materials. We have thus developed a new coating which is able to stop bacterial adhesion and multiplication, while being biocompatible with fibroblasts.[4]

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ACKNOWLEDGEMENTS: We are grateful to Regine Landmann, UniBS, for microbiological investigations, A. U. Daniels, UniBS, for calorimetric measurements, T. de los Arcos, UniBS, for XPS, Marco Celio, UniFR, for fibroblast cells, Claudio de Virgilio, UniFR, for yeast cells, as well as the SNF for financial support (NCCR Nano & interdisciplinary research fund).

Adhesion Lifetime Prediction of Diamond-Like-Carbon (DLC) Coatings on Biomedical Implants

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INTRODUCTION: Coating delamination is one of the principal causes of failure in coated articulating biomedical implants [1]. The lifetime of the coated implant depends on the magnitude of the load applied at the interface (e.g. residual stress, coating thickness), but also on the stability of the interface in corrosive media such as body liquid. While fast delamination of the order of hundreds of μm/day can easily be observed, very slow delaminations of the order of a few μm/year are very difficult to detect. Nevertheless, several delaminating microscopic spots growing with just a few μm/year can determine the failure of the coated implant after several years. Although many qualitative studies of the mechanisms involved in DLC coated implant failure exist [2,3], to our knowledge no quantitative analysis of coating adhesion lifetime on biomedical implants has ever been done up to now.

METHODS: Submicron as well as several microns thick DLC layers have been deposited on BioDur™ CCM Plus™ biomedical implant alloy substrates provided by Carpenter Technology Corporation using the RF (13.56 MHz) Plasma Activated Chemical Vapor Deposition (PACVD) method with acetylene (C_2H_2) as process gas. In order to promote a better adhesion of the DLC coatings, ~ 90 nm thick Si containing DLC and several metallic (Cr, Nb, etc.) interlayers have been deposited prior to DLC using the combined PACVD and magnetron sputtering techniques. The coating delamination was induced by the Rockwell indentation method. The time evolution of the delamination in phosphate buffer solution (PBS) at 37 °C around the indentation was quantified by means of optical investigations of the propagating crack and finite element method (FEM).

RESULTS: The coating delamination around the Rockwell indentation is controlled by stress-corrosion cracking (SCC) mechanism since it shows a strong dependence on both stress and environment. High-resolution scanning (SEM) electron microscope investigations of the transversal cuts performed by means of focused ion beam (FIB) revealed that the propagating crack front occurs at the interface between the DLC and CoCrMo substrate (Fig. 1-(a)). The quantitative

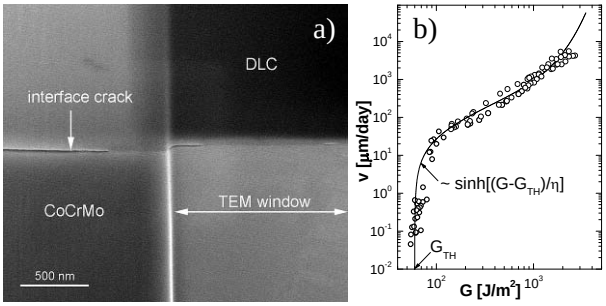

Fig. 1: SEM micrograph of a FIB transversal cut, showing the interface crack (a); SCC curve for DLC/CoCrMo interface in PBS at 37 °C (b).

SCC (G,v) curves are fitted with the reaction rate model [4] used to explain the crack propagation in bulk ceramics and glasses (Fig. 1-(b)):

$$v(G) = (v_0/B)\sinh[(G-G_{TH})/\eta], \qquad (1)$$

where v_0/B, η and G_{TH} are material dependent macroscopic crack velocity parameters. The (G,v) curves, such as the one in Fig. 1-(b), allow to determine the speed of delamination and adhesion lifetime of any DLC coating if the thickness and residual stress are known. Thus, DLC coatings with different interlayers (Si-DLC, Cr, Nb, etc.) showed adhesions up to 100 times better than those without interlayer. However, a strong dependence of the adhesion on the O_2 content in the deposition chamber was observed. Thus, by reducing the O_2 background pressure in the chamber from 5×10^{-4} mbar to 1×10^{-4} mbar, the adhesion is improved by a factor ~ 7.

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In vitro and *in vivo* Testing of a Novel Zirconia Implant Surface for Dental Applications

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INTRODUCTION: Dental implants are a successful and reliable treatment method for the fully or partly edentulous patient. For esthetical reasons there is an increasing demand for tooth colored implants, i.e. made out of zirconia. The nature of the dental implant surface, where the most important surface properties are topography and surface chemistry, is of critical importance for a successful osseointegration. Evaluating a new potential surface for implant application (i.e. made out of zirconia), extensive *in vitro* and *in vivo* testing has to be performed prior to clinical application.

METHODS: Zirconia samples (Y-TZP) were sandblasted and half of the samples were additionally alkaline etched. A sandblasted and acid etched titanium surface was used as a reference. Characterisation of the surfaces was performed by SEM and confocal white light microscopy describing the surface topography and with XPS analyzing the chemical composition of the surface. *In vitro* testing was performed with SAOS-2 osteoblast-like cells cultured on the different surfaces. Cell morphology was investigated by SEM and fluorescence imaging. Cell number-relevant parameters and osteogenic differentiation factors (i.e. ALP and calcium accumulation) were determined. *In vivo* testing was done in the minipigs mandible with dental implants made out of zirconia and titanium with the described surfaces. After 4 and 13 weeks of unloaded healing, the bone to implant contact (BIC) was determined histologically; mechanical anchorage in the bone was quantified by torque out measurements.

RESULTS: For all surfaces moderate surface roughness [1] was obtained (using SEM and confocal light microscopy), where titanium showed the highest roughness values. The chemical composition of the surface (XPS) was not changed by the etching process. *In vitro* experiments revealed a better spreading as well as higher number of adherent cells after 24 h incubation on zirconia surfaces compared to titanium. Also, the cellular metabolic activity after 24 h and the proliferation rate after 48 h were higher on zirconia compared to titanium. Zirconia had a more pronounced effect compared to titanium on the differentiation of SAOS-2 cells: ALP activity, an early differentiation marker and mineralization, a late differentiation marker, both increased. Only minor differences in calcium accumulation were found between zirconia with sandblasted and with sandblasted/etched surfaces; sandblasted/etched zirconia promoted differentiation slightly better. Osseointegration *in vivo* was successful, with mean BIC not significantly different between the three surfaces after 4 weeks. BIC turned out to be significant after 13 weeks, with a higher BIC for titanium. Removal torque was significantly different between all three surfaces after 4 weeks. After 13 weeks, both zirconia surfaces showed similar removal torque values, whereas titanium again exhibited significantly higher values compared to zirconia surfaces.

DISCUSSION & CONCLUSIONS: *In vitro* data indicate that zirconia mediates a pronounced better effect on the adhesion, proliferation and differentiation compared to titanium; and that topographical differences of zirconia have minor effects on osteoblast biology. However the *in vivo* results show that the tested zirconia surfaces could not consistently achieve mechanical anchorage and osseointegration comparable with sandblasted and acid etched titanium surfaces.
It is concluded that material and surface roughness have a significant influence on *in vitro* and *in vivo* performance; however the results must not be congruent.

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Osseointegration of ZrO_2 Dental Implants in Comparison to Standard Titanium Implants.

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[3] *Private Dental Clinic, Munich, Germany*

INTRODUCTION: Tooth replacement with dental implants has become a well accepted treatment technique. Nowadays the patient's aesthetic demands have increased and the use of zirconia implants has become an attractive alternative to titanium because of the material's tooth like colour.

The objective of the present study was to histomorphometrically investigate the amount of direct bone implant contact and peri-implant bone density for ZrO_2 implants with a new rough surface topography in comparison to Ti-SLA implants.

METHODS: Fifteen cylindrical zirconium implants 4.1 mm in diameter and 10.5 mm in length with an acid etched surface together with 15 Ti-SLA implants of the exact shape were implanted in pig maxillae.

After 4, 8 and 12 weeks the animals were euthanized and implants with the surrounding bone, were removed, fixed and embedded in MMA. Serial sections were obtained, x-rayed, stained with Toluidine blue, and histomorphometrically analysed.

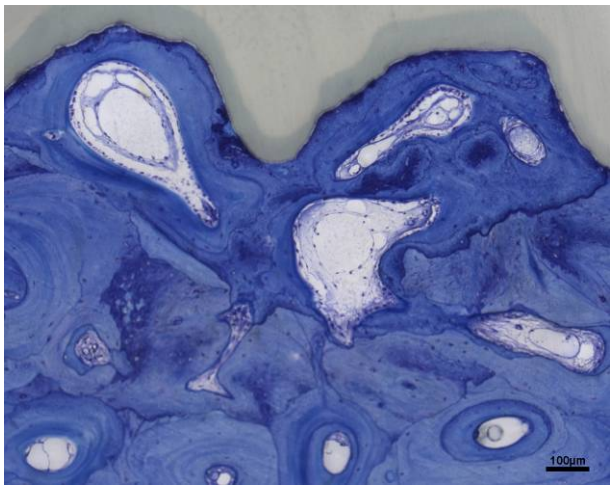

Fig. 1: Complete osseous integration of a ZrO_2 implant (grey); the bone is stained blue with toluidine blue. Note that there is no difference in osseointegration compared to the Ti-SLA implant in Fig. 2.

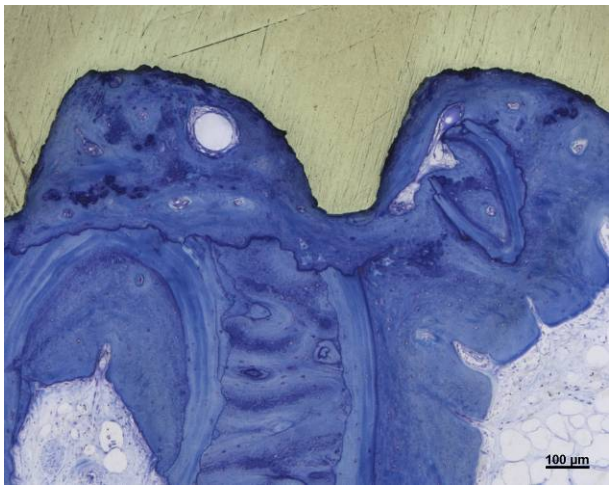

Fig. 2: Osseous integration of a Ti-SLA implant. There is complete coverage of the implant surface with bone tissue (blue).

RESULTS: Histological evaluation showed direct osseous integration for both materials (Fig. 1, 2). ZrO_2 implants revealed mean peri-implant bone density values of 42.3% at 4 weeks, 52.6% at 8 weeks, and 54.6% at 12 weeks after implantation, whereas Ti-SLA implants demonstrated mean values of 29%, 44.1% and 51.6% at corresponding time intervals. Concerning bone interface contact ratio the mean values for ZrO_2 ranged between 27.1% and 51.1% and between 23.5% and 58.5% for Ti-SLA.

DISCUSSION & CONCLUSIONS: The histological results did not reveal any statistically significant differences between both materials at any given time point.

This result in our opinion indicates that the ZrO_2 implants have a comparable capacity for osseous integration as the titanium implants from the control group.

It however must be stated that the number of specimen per group is too low, to allow to simply extrapolate the results to the situation in the human patient.

Oxide Ceramics in Endoprosthetics

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ABSTRACT: Ceramic materials for load bearing implants have played an important role for more than 35 years.

The pure ceramic material Al_2O_3 was introduced into the market by Boutin in 1969/1970. He was the first surgeon who implanted alumina hip heads in cups for hip prostheses. 15 years later in 1985 ZrO_2 (Y-TZP) especially for hip joint heads was introduced. Y-TZP showed a higher mechanical strength and fracture toughness compared to alumina. The bending strength of Y-TZP is approximately twice and the fracture toughness about three times higher compared to alumina. Reasons therefore are the much finer grain size and the transformation toughening mechanism tetragonal → monoclinic of the Y-TZP material. For common used zirconia for orthopaedic devices the grain size is about 0.5 µm compared to bio grade alumina with approximately 2 µm. By using zirconia it is possible to realize ceramic components with thinner wall thickness and more complex geometries like ceramic knee prostheses. But the big disadvantage of pure Y-TZP is its lower stability against low temperature degradation (LTD)[1]. Under hydrothermal conditions an unwanted phase transformation to monoclinic zirconia at the surface of the ceramic implants can occur. This is combined with an increase of the surface roughness and a decrease of the strength. By this the application of Y-TZP has been discussed very controversially in the last years and due to the decreased acceptance the market share for zirconia implants is low.

A way of combining the positive properties of Al_2O_3 (wear resistance, hydrothermal stability and hardness) with those of ZrO_2 (strength and fracture toughness) are the dispersion ceramics Alumina Toughened Zirconia ATZ and Zirconia Toughened Alumina ZTA. Such dispersion ceramics were introduced into the market in 2002.

With increasing zirconia content the strength and toughness can be improved compared to pure alumina. On the one hand material data of the dispersion ceramics ATZ and ZTA like flexural strength, fracture toughness, microstructure, hardness etc. will be shown[2, 3].

On the other hand the influence of the material properties on the in vitro behaviour of ceramic implants will be presented.

Especially for the application as articulating components of artificial hip joints the burst strength according to ISO 7206-10 and the wear performance in a hip simulator according to ISO 14242 were determined[4].

As a main point the often discussed ageing behaviour of Zirconia respectively zirconia containing ceramics under hydrothermal conditions (LTD – Low Temperature Degradation) of the dispersion ceramics was investigated[5].

By adding of alumina the resistance of zirconia against low temperature degradation is strongly enhanced. It is possible to suppress or lower the phase transformation tetragonal → monoclinic on the surface.

Using dispersion ceramics offers new choices for artificial joints. ZTA is suitable for implants with higher strength than alumina. ATZ ceramic is the best solution for high-performance demands with complex geometries and high reliability.

Both groups of dispersion ceramics will have a high potential for applications in endoprosthetics.

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Titanium-Zirconium: A novel Material for Dental Implants

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INTRODUCTION: The choice of implant material has a high impact on the resulting mechanical and biological properties. Pure titanium is known for its biocompatibility and its resistance to corrosion. However, its mechanical properties are limited in the case of small diameter implants. A new material for dental implants with the brand name "Roxolid" was developed to overcome the mechanical limitations of pure titanium.

PHYSICAL, CHEMICAL & BIOLOGICAL PROPERTIES: The new material is composed of the two elements titanium and zirconium. This binary TiZr alloy has a significantly increased mechanical stability compared to titanium grade 4 with respect to elongation and fatigue strength. Internal measurements show that the ultimate tensile strength is comparable to Ti-6Al-4V. The TiZr implants are manufactured with the SLActive surface like the titanium SLActive implants: Sand blasted, acid etched and then stored in 0.9% NaCl solution in order to maintain the clean oxide layer with its hydrophilic properties. The TiZr SLActive implants have a water contact angle of 0° like the Ti SLActive implants. The scanning electron micrographs in figure 1 show that the same surface structure is obtained on both materials. In general, the SLActive surface has a significantly improved osseointegration compared to the conventional SLA implants packed and stored under ambient conditions.

Many metals are known to strongly inhibit growth of osteoblasts (e.g. V and Nb), whereas Ti and Zr do not [1]. Therefore Ti and Zr have preferred osseointegration capabilities. In a biomechanical and histological study in the mandible of 12 miniature pigs Ti SLActive and TiZr SLActive were compared using specially designed implants for removal torque (RT) measurement and bone-chamber implants for histological observations. After 4 weeks of healing, RT evaluation indicated significantly higher values ($p = 0.02$) for TiZr (230.9 ± 22.4 Ncm) in comparison to Ti (204.7 ± 24 Ncm). Histology (toluidine blue) showed that new bone of woven type with a noticeable area of composite bone was invariably present inside the Ti and TiZr implant chambers. Bone trabeculae originating from the edges of the experimental defect followed the osteoconductive surface of the chamber towards its most centripetal aspect. Early stages of haversian systems formation were noticed driven by the presence of mature vessels. The histomorphometry showed a bone to implant contact (BIC) of 75.4 ± 21.3 % for Ti and 74.6 ± 15.3 % for TiZr and a bone density of 50.4 ± 19.1% for Ti and 47.2 ± 12.3 % for TiZr.

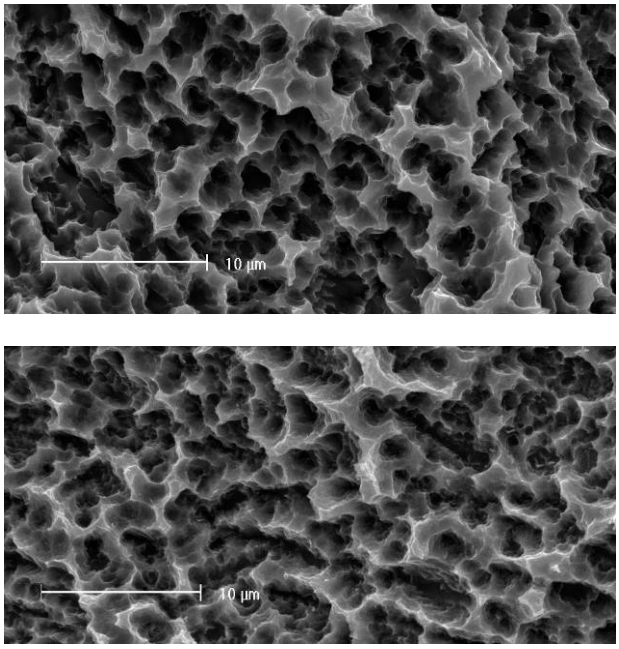

Fig. 1: Scanning electron micrographs of Ti SLActive (top image) and TiZr SLActive (bottom image).

CONCLUSIONS: The TiZr alloy called "Roxolid" combines high mechanical strength with excellent osseointegration and is thus well suitable for dental implants with narrow diameters.

REFERENCES: [1] S.G. Steinemann (1998) *Periodontology 2000* **17**:7-21.

ACKNOWLEDGEMENTS: We thank Marcel Obrecht and Lars Sennerby for their contributions.

In vitro Degradation of a Magnesium Alloy in Simulated Body Fluid: Influence of Heat Treatment and Plastic Deformation

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INTRODUCTION: In recent years, magnesium has awakened interest in the field of bioabsorbable implant materials [1]. The fact that Mg degrades at pH values below 11.5 [2], that it is an essential element in the human body and its body compatibility, make magnesium a suitable candidate for such applications. However, in the human body (pH ≈ 7.4) a magnesium implant might degrade too quickly and lose its mechanical strength before the tissue has fully healed. Various techniques have been developed to improve the corrosion resistance. A possible method besides the choice of suitable alloys containing corrosion-inhibiting elements is the deployment of heat treatments at high temperatures causing protective oxide layers to form [3].

We studied the bio-degradation behaviour of a Mg–Y–RE alloy in different heat treatment states by electrochemical impedance spectroscopy (EIS) and immersion testing in a simulated body fluid (SBF). As during implantation the material might be deformed and the thermal oxide layer damaged, we intentionally strained the samples and analysed the degradation behaviour of such cracked oxide layers.

METHODS: For this study an extruded bar of WE43 was investigated (ca. 4 wt-% Y, ca. 3 wt-% RE and > 0.4 wt-% Zr). For EIS and immersion testing polished disks were prepared. Some specimens were heat treated at 525°C for 5 h and then water quenched (solution heat treated state, sht) causing the formation of a surface oxide layer. To analyse the influence of plastic deformation on the degradation performance of oxidised samples, flat bar tensile specimens were machined and solution heat treated. Then, they were strained to 9%. A detailed description of the preparation process of the samples is given in [4].

RESULTS: The heat treatments performed caused the formation of a thermal oxide layer on the sample surfaces, which consisted mainly of Y_2O_3 and which slowed the degradation and increased the polarisation resistance significantly. However, in some specimens localised corrosion attacks occurred which drastically weakened the protective effect of the oxide.

The strained oxidised samples degraded more than their non-strained oxidised counterparts, but they performed still better than the polished specimens. Macroscopically, the degradation process appeared homogeneous. But on a microscopic scale local corrosion attacks were observed, which started at the cracks and led to undermining of the oxide layer (Fig. 1a). With time cracked oxide layer fractions in between the cracks fell out, as indicated in Fig. 1b showing a sample after 7 d of immersion in SBF.

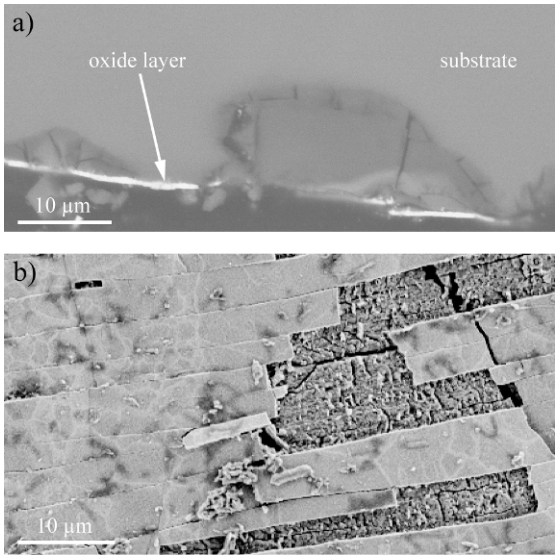

Fig. 1: SEM micrographs of a sht oxidised sample strained to 9% after 7 d of immersion: a) cross-section and b) surface.

DISCUSSION & CONCLUSIONS: The heat treatment at high temperature caused the formation of a protective oxide layer, which slowed the degradation compared to the polished state. This oxide layer still fulfils its function, even if it is damaged and if there are cracks in the layer. However, corrosion attacks start at these cracks.

REFERENCES: [1] F. Witte, J. Fischer, J. Nellesen, et al (2006) *Biomaterials* **26**:3557-63. [2] M. Pourbaix (1974) *Atlas of Electrochemical Equilibria in Aqueous Solutions*, National Association of Corrosion Engineers. [3] A.C. Hänzi, P. Gunde, M. Schinhammer et al (2009) *Acta Biomater* **5**:162-71. [4] P. Gunde, A. Furrer, A.C. Hänzi et al (2009) *J Biomed Mater Res A*, in press.

Development of a Low Wear and Ageing Resistant UHMWPE

R Lerf

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INTRODUCTION: Worldwide, more than 500'000 hip joint prosthesis are implanted every year. In most of the cases, this treatment is a long-term clinical success and patients are pain-free and fully mobile. However, there are revision surgeries. The most frequent reason for revision of hip joint implant is aseptic loosening. I.e., PE wear particles from UHMWPE, the most widely used bearing material in joint replacement, have lead to degradation of the bone and loosing of the prosthesis. By cross-linking UHMWPE, an important step in reduction of PE wear was achieved about 10 years ago. In clinical studies, a lowering of the wear rate up to 80 % after 5 years was found[1].

Consequently, another weak point of UHMWPE becomes the life time limiting factor: Ageing resistance. The present work describes the development of a low wear, oxidation resistant UHMWPE by adding a natural anti-oxidant, vitamin E.

METHODS: Based on a material requirement specification, a development process was started which focused on materials aspects and consolidation technology in parallel. The influence of chemical composition, sintering parameters, thermal treatments and cross-linking energy on the mechanical properties, the wear behaviour and ageing resistance was investigated.

The results of a large number of mechanical, physical and chemical tests, as well as screening wear tests helped to define the chemical composition and the sintering parameters. For the assessment of the thermal treatment and the cross-linking procedure, extensive hip simulator studies were conducted.

RESULTS: Unlike other cross-linked UHMWPE, vitamys exhibits mechanical properties according to ISO 5834 type 1 resin (GUR 1020), cf. table 1. Compared to non cross-linked GUR 1020, only the ultimate tensile strength undergoes a moderate decrease. Wear properties are markedly improved. Compared to conventional UHMWPE, a reduction of wear rate by a factor of 3 is found in OrthoPOD pin-on-disc testing. In the hip simulator study, the corresponding wear rate was found to be diminished by a factor of 5, using calf serum diluted to 30 g/L as lubricant.

In accelerated ageing experiments (5 bar O_2 at 70 °C), the procedure was stopped after 60 days without finding any oxidation in vitamys. At that time GUR 1020 had reached an oxidative index (OI) of 4.6. (Oxidative index > 1.0 means severe embrittlement.) The more aggressive ageing in 5% H_2O_2-$FeCl_3$ solution at 50 °C for 42 days yielded an OI of 0.84 for vitamys and 8.4 for GUR 1020, respectively (Figure 1).

Table 1: Results of tensile and wear testing of vitamys compared to GUR 1020 sheet material and the corresponding standard.

	vitamys	GUR 1020	ISO 5834-2, type 1
$R_{p0.2}$ [MPa]	22.8	22.6	≥ 21.0
R_m [MPa]	36.5	45.7	≥ 35.0
A [%]	392	374	≥ 300
OrthoPOD [mg/Mc]	0.7	2.0	-
Hip simulator [mg/Mc]	5.9	29	-

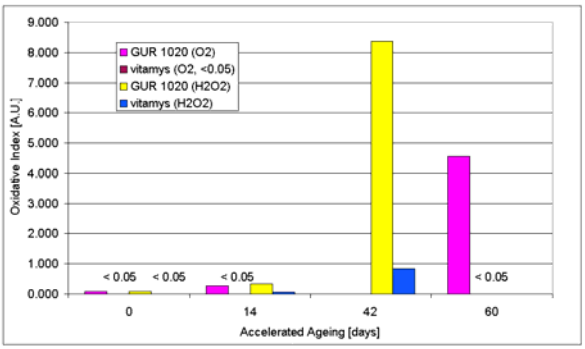

Fig. 1: Effect of accelerated ageing on oxidation of UHMWPE: 0.1 % vitamin E protects effectively against oxidative degradation.

DISCUSSION & CONCLUSIONS: vitamys is a new generation of cross-linked UHMWPE for hip joint articulation with a superior combination of mechanical properties, an extreme ageing resistance and a wear rate equivalent to state-of-the-art cross-linked PE, when tested under comparable hip simulator conditions[2].

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Vitamin E as an Antioxidant in Implants
Concentration Determination in GUR® / Alpha-Tocopherol Blends

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INTRODUCTION: Alpha-tocopherol stabilization of GUR® UHMWPE implants for total joint replacements is one of the major trends in current development efforts. A large number of scientific papers have been published on this subject and the commercialization process of alpha-tocopherol containing implants has already started.
The desired concentration ranging from trace amounts like e.g. 200 ppm to high levels like e.g. 5000 ppm has been discussed for quite some time. At the same time the concentration determination in UHMWPE powder as well as in the final implant has been a subject of research activities.

METHODS: The described determination method for alpha-tocopherol contained in GUR® UHMW-PE powder can be subdivided into different steps: extraction, HPLC separation and UV detection.
For the extraction step a small amount of alpha-tocopherol containing material is boiled with methanol under reflux for a few hours. The solution is then filtered over a 0.45 µm filter. For the determination of the extracted alpha-tocoperol an analytical HPLC system with UV detector was employed. Zorbax Eclipse XDB-C8 (or comparable) columns were used at 50 °C and the eluent was a 95 / 5 methanol / water mixture. The vitamin E concentration is determined at the 291 nm absorption band.

RESULTS: For the validation of the UV detection, solutions with different alpha-tocopherol concentrations ranging from 0.5 to 1000 ppm were used.

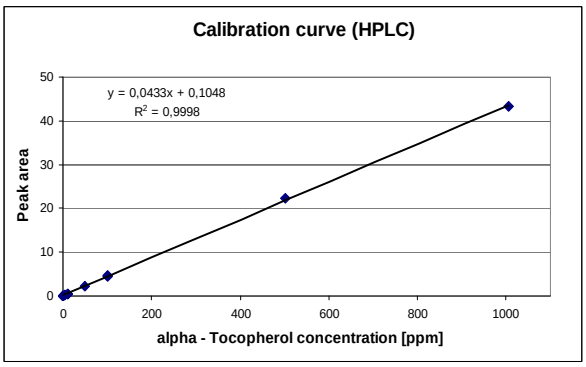

Figure 1: Calibration curve for UV detection

The graph illustrates the excellent linear correlation between the vitamin E concentration and 291 nm peak area. The lower limit for the concentration determination was found to be 1 ppm while the detection limit is 0.5 ppm.
In a second step the retrieval of the extraction process was tested. Different amounts (5 to 50 ppm) of vitamin E were added to GUR® 1020 powder already containing 500 ppm. The additive was then extracted by the method, described and an average retrieval rate of 93% was found.
Reproducibility of the method was tested by measuring 27 identical samples (Figure 2). As an average 961 ppm of alpha-tocopherol were found in the powder sample. The standard deviation of the measurement is 35.6 ppm (3.7 %).

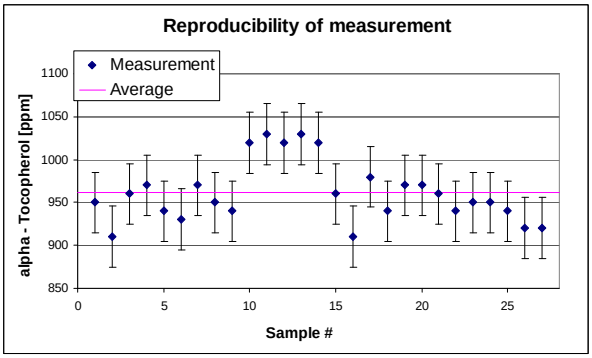

Figure 2: Reproducibility assessment

DISCUSSION & CONCLUSIONS: The described method shows a new approach to reliably and accurately determine alpha-tocopherol concentrations in UHMW-PE (GUR®) powder especially for low concentration ranges.
Tests with molded sheets have been started recently; the first results look very promising so that the method can be applied to semi-finished goods, also. The loss of alpha-tocopherol due to heating during compression molding or any post treatment can be checked with this method, too.

X-ray Markers for Resorbable poly(hydroxy carboxylic acid) Osteosynthesis Implants

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INTRODUCTION: Due to the low density of polymers used for osteosynthesis implants their x-ray density is low. Therefore they cannot be detected sufficiently by conventional x-rays. On the one hand this is an advantage because bone below the implant remains visible and examinations such as MRT can easily be carried out. On the other hand there is a need to control the position of the implant and to follow its degradation by x-ray inspection. This problem can be solved by blending x-ray markers, i. e. materials having a high density, to the polymer matrix**.**

METHODS: The most commonly used polymers for osteosynthesis implants are *polylactide* (PLA), *polyglycolide* (PGA), *polycaprolactone* (PCL) and co-polymers thereof. As representative matrix materials for the compounding experiments with four different x-ray markers (*Tab. 1*), 85/15 Poly(L-lactide-co-glycolide), a PLA co-polymer, and ε-PCL were chosen. Mechanical properties and the x-ray contrast were preferably investigated with the *polylactide* and flow and mechanical properties with the *polycaprolactone* compounds.

Table 1. Properties of x-ray markers

	Molar mass g/mol	Grain size µm
Hydroxylapatite	502.32	2.0 - 4.0
Bariumsulfate	233.40	0.5 - 1.0
Strontiumcarbonate	167.63	< 0.5
Zirconiumoxide	123.22	1.5 - 3.0

The compounding of the powders into the matrix polymers was carried out on a type ZSE 18 HP lab extrusion equipment by Leistritz. Thereafter, standard type 1A test samples according to EN ISO 527-2 have been manufactured on an Arburg Allrounder 270 S injection moulding machine.

RESULTS: In a first step the minimum filler concentration to achieve a sufficient x-ray contrast was determined on PLA. It turned out that a content of 5 %-w/w was visible for all powders (except for hydroxylapatite – 20 %-w/w) for good x-ray imaging of the test samples in a preliminary experiment (Fig. 1).

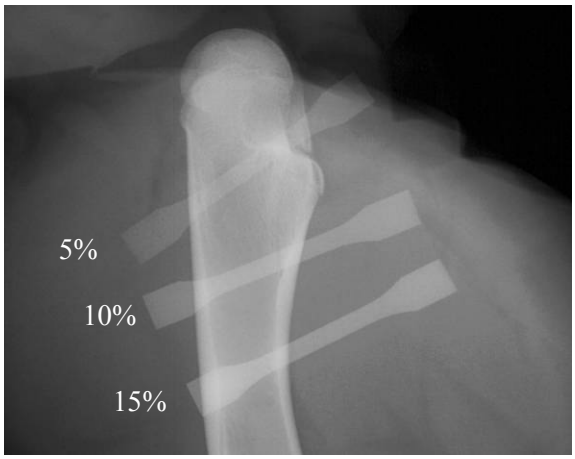

Fig.1: X-ray contrast for PLA with bariumsulfate

The compounding accuracy in all cases was high (*Tab. 2*) and the particle distribution very homogeneous (*Fig. 2*).

Table 2. Nominal and effective x-ray marker concentrations in PCL

	Filler concentration (%-w/w)	
	nominal	effective
Hydroxylapatite	20.0	22.1
Bariumsulfate	5.0	5.0
Strontiumcarbonate	5.0	5.7
Zirconiumoxide	5.0	5.1

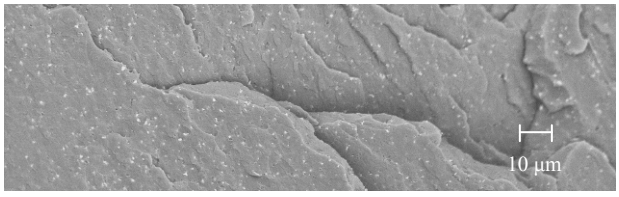

Fig. 2: Particle distribution (small white dots) in PLA containing 5% $BaSO_4$, magnification 1500x

DISCUSSION & CONCLUSIONS: It could be shown that already for a filler concentration of 5 %-w/w an x-ray contrast sufficient for the described indications could be achieved. For this concentration, independent of the filler type, the mechanical and flow properties differ only little from those of the pure matrix materials, so that the functionality of the implants remains unchanged and the manufacturing process requires only little adjustment.

Experiences and Future Development of icotec Continuous Carbon Fibre PEEK Implants

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INTRODUCTION: icotec AG stands for composite implant development and production using continuous carbon fibre reinforced PEEK for load bearing applications in orthopedics and spine surgery.

The CF/PEEK properties allow realization of new philosophies in orthopedic treatment.

ICOTEC MATERIAL PROPERTIES: icotec composite implants unify four major advantages: mechanical properties comparable to TiCP grade IV, a moderate Young's modulus of 40 to 70 GPa, artifact free imaging in conventional radiology, CT and MRI and a design freedom specific to the icotec production process.

MECHANICAL PROPERTIES: Depending on the carbon fibre orientation in the final implant ultimate strength reaches >900 MPa (see Fig.1). Fatigue properties typically reach 60% or more of the initial static values.

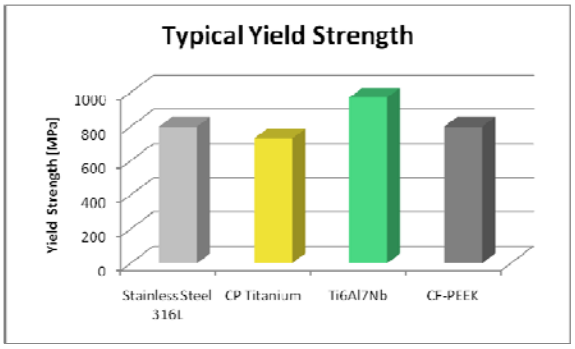

Fig. 1: Yield strength of icotec rods and metal bars.

MATERIAL MODULUS: Stiffness of icotec composite implants depends heavily on the implant design and on the fibre orientation. Typical modulus of elasticity for bending is in the range from 40 to 70 GPa.

IMAGING CHARACTERISTICS: The radiological properties of CF/PEEK reduce artifacts in imaging diagnostic procedures and provide more information and comfort to the surgeon. The surgeon gets more information about the region of interest (fracture zone), intra-operatively as well as in the post-operative healing phase.

DESIGN FREEDOM: The patented production process of icotec allows a sophisticated functional implant design that respects the anatomical and bioengineering conditions.

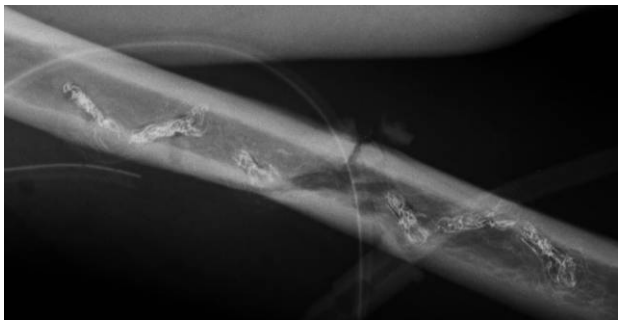

Fig 2: Typical x-ray of icotec Snakeplate on a humerus

FUTURE IMPLANT DEVELOPMENT:
Clinical experiences with the icotec Snakeplate in fracture treatment have confirmed the experimental data. The composite material has shown outstanding performance in the application of numerous spinal and trauma implants.

The unique combination of high strength with lower stiffness may fulfill the requirement for more dynamic implants and for implants that better match conditions for bone healing.

Long-term implants with requirements for optimal osseointegrative functions can now be coated with various techniques. Extensive evaluation has proven the dramatic improvement of direct bone contact with titanium coated implants.

In close collaboration with partners in the orthopedic market new implant systems are under development.

REFERENCES: B. Rohner, et al. (2005) Performance of a composite flow moulded carbon fibre reinforced implant; *Veterinary and Comparative Orthopaedics and Traumatology* **18**:175-82

Rapid Manufacturing of Individualized Ti-6Al-4V Bone Implants

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INTRODUCTION: Rapid Manufacturing (RM) has become a key technology for producing high quality parts within hours. Moreover it's probably the only economic option to produce parts in small quantities. The idea to adapt RM laser-based layer processes to produce individualized bone implants showed to be a promising way to meet the requirements of individual and patient-specific orthopaedic treatment. However, RM produced implants initially cannot be compared with conventionally abrasive manufactured parts. Due to the complete melting of small powder particles and the large local energy induced by the laser beam, problems like residual stress, deformation, loss of density and smaller tensile strain may occur. To get the approval for such new processed materials, further RM process improvements have to put the focus on achieving mechanical properties which are comparable to known material standards.

METHODS: Selective Laser Melting (SLM) is a Rapid Manufacturing technique which enables direct fabrication of complex metallic parts with high bulk density. Titanium powder is spread out and scanned by a continuous wave Ytterbium (100W) fibre laser. This layer-by-layer melting process ends in perfect reproduction of previously designed implant datasets. SLM needs demanding control [1]. The process itself consists of many different parameters which all have influence on the quality of the outcome (*see fig. 1*). But also thermal post treatment processes have an effect on the resulting material properties. This project investigates the density and the tensile strain of processed parts, influenced by laser power, exposition time and focus lens position in combination with different thermal post treatments.

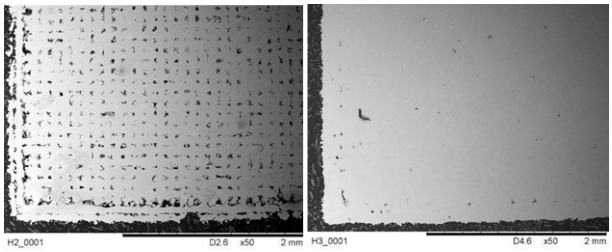

Fig. 1: Scanning Electron analysis of the macrostructure of SLM processed Ti6Al4V cubes. Left: Low laser power. Right: High laser power.

RESULTS: It is possible to use CAD designed or anatomically shaped datasets to transform them directly into metallic structures. Depending on given process and post treatment parameters, the mechanical properties can be significantly influenced. Metallographic studies on SLM cubes showed, that higher laser power, adequate exposure time and slightly shifted lens position ends in high bulk density. Heat treatment (*see fig. 2*) at 925°C for 4 hours with cooling ramps down to 760°C at a rate of 50°C/h and finally cooling down to room temperature at 360°C/h in argon atmosphere showed best mechanical properties. The elongation at break could be improved by a rate of 300%.

Fig. 2: Left: Native SLM processed tensile probes. Right: Probes after heat treatment in argon atmosphere at 925°C for 4 hours.

DISCUSSION & CONCLUSIONS: SLM processed Ti-6Al-4V show a significant difference in mechanical properties compared to conventionally processed materials. The outcome can be enhanced with carefully selected process parameters and thermal post-processing in an inert gas atmosphere. Further examinations have to be done in order to reach higher density and tensile strain. Therefore the focus will be put on the scanning strategies and the overlap of laser lines, while scanning the powder surface.

REFERENCES: [1] Kruth JP.; Froyen L.; Van Vaerenbergh J.; Mercelis P.; Rombouts M.; Lauwers B. (2004): Selective Laser Melting of iron-based powder. *Journal of Materials Processing Technology* **149**:616-22.

ACKNOWLEDGEMENTS: This project was supported by the FHNW Research Foundation and the Förderverein Fachhochschule Nordwest-schweiz Solothurn.

Biologically Inspired Surface Modification of Metal Implants Through Ultra-Thin Coatings

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[2] *Laboratory for Surface Science and Technology (LSST), D-Matl, ETH Zürich, CH*

INTRODUCTION: The first interaction between a biological system and an artificial implant occurs on its surface. Therefore a crucial aspect in the design of biomaterials is the definition and the control of implants surface properties. Polymers and metal (oxides) have been shown to non-selectively adsorb a large quantity of proteins in their native state (fig. 1A). To reduce this non-specific response and inspire a selective answer surface modifications based on ultra-thin coatings have been proposed: (i) adsorption of self-assembled monolayers (SAM) to control the physicochemical properties (fig. 1B); (ii) immobilization of "non fouling" or biologically inert polymers (fig. 1C); (iii) modification of non fouling surfaces with biomolecules to address selective interaction with cells and tissues (fig. 1D)[1].

MODIFICATION OF METAL SURFACE: A way to tailor the physicochemical properties (e.g. electrical charge or hydrophilicity) of biomaterials, and thus passively influence the interaction with biological species, is achieved through spontaneous adsorption and arrangement of single layers of molecules.

Several ways to create protein resistant (i.e non fouling) surfaces have been proposed: among them the most popular approach is based on the use of Poly(ethylene glycol) (PEG), which acts as a barrier, due to a synergy of different aspects, including osmotic and entropic repulsion effects, and high water content. Even more interesting is the combination between such adlayers, and some specific bio-ligands (e.g. short peptide sequences) linked covalently to the non fouling surface.

Among the different systems used to achieve protein resistance, a newest and more effective approach, in terms of layer binding strength, inspired by the activity of a cyanobacteria has been recently presented: a fragment of Anachelin, a molecule normally secreted by these microorganisms to collect iron ions from the environment, was conjugated to PEG and bound to titanium oxide surfaces[2], generating a stable, non fouling system.

The covalently immobilization of polymers and biomolecules on surfaces can be also achieved via a photoactive heterobifunctional crosslinker[3], which acts like a "molecular glue" when illuminated at a certain wavelength. This process, based on a simple chemistry has been tested to be effective in a very wide range of applications and appears very promising also in biomedical areas.

OUTLOOK: Different strategies enabling a better control of biomedical interfaces have been showed. Further information related to the industrial up-scaling of such laboratory techniques will be presented along our contribution.

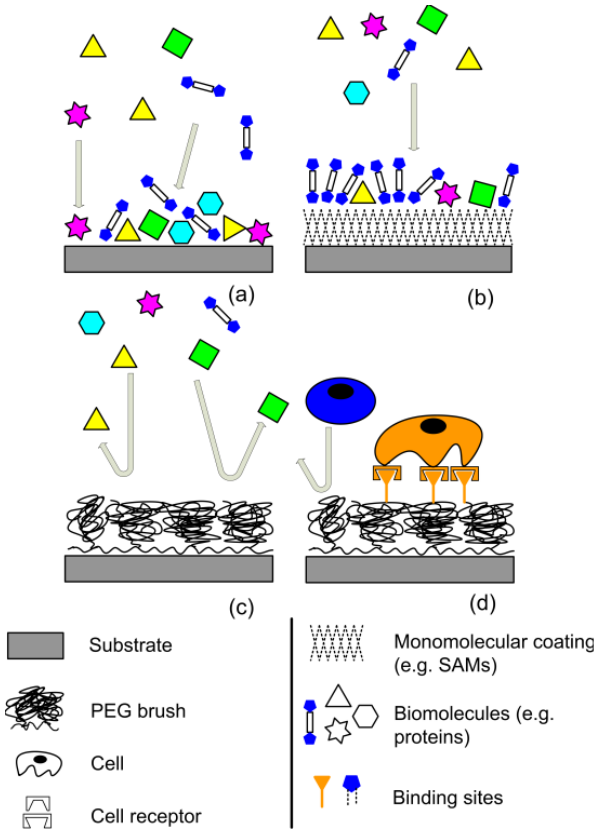

Figure 1:Processes taking place at the interface between an implant (with or without surface modifications) and a biological environment

REFERENCES: [1] Schuler et al. (2006) *Nanomedicine* **1 (4)**. [2] Zürcher et al. (2006) *J. Amer. Chem. Society*, **128 (4):**1064-5. [3] Liu et al. (2006). *J. Amer. Chem. Society* **128**:14067-72.

Significance of Cleanliness of Medical Devices

M Rasori

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INTRODUCTION: Medical components cleaning (implants, instruments, etc.) is often regarded as a necessary evil in industry and is often added on at the end of the existing production lines, without any attempt to look at the production process as a whole and integrate cleaning operation in that process. The technical cleanliness of components, their functional surfaces and the production environment are absolutely essential, however, for the manufacture of high-quality medical products.

METHODS: The choice of the cleaning technique has become more complex for various reasons. Various legal requirements require a drastic change of the cleaning methods. The demand for higher cleanliness of parts is growing. The problem the medical sector is confronted with, consists in an absolute necessity for clean surfaces which are not only free of polar (e.g. salts) but also of non-polar (e.g. oils) soilings.

The use of detergents is limited due to the fact that they will be rapidly saturated by cutting oils, thus reducing their cleaning power. Oil separators and the automatically metered addition of detergent components however, improve their efficiency. Degreasing in open tanks of chlorinated solvents was a simple and efficient way to clean parts. But it was also highly polluting the environment and toxic for the operators. This method has been replaced by fully encapsulated machines using non chlorinated AIII hydrocarbon solvents under vacuum.

Nowadays, preliminary and intermediate cleaning systems in the field of medical technology are often based on AIII solvent cleaning. AIII solvents are hydrocarbons, either modified alcohols or isoparaffins, with a flash point of between 56 and 100°C. They are extremely stable where their storage life is concerned, leave a protective film that is approximately 2 to 13 nanometers thick and can be recycled using vacuum distillation. This system enables the fully automatic cleaning, steam degreasing and drying of components. Cleaning quality is further enhanced by ultrasound and microfiltration.

In order to be able to guarantee the required level of biocompatibility, the final cleaning process is carried out using water-based ultrasound immersion cleaning systems. Here, the water-based cleaning complies with a series of complex requirements, such as

- Intensive, yet gentle cleaning of various materials.
- Complete removal of various impurities, e.g. swarf, polishing agent residues, grinding residues, salts or minerals.
- Activation or passivation of material surfaces and their preparation for all types of subsequent processing.

Fig 1: Amsonic Cleaning unit, Amsonic 4000

RESULTS: Thanks to state-of-the-art cleaning systems, user-friendly controls and extensive know-how in the field of validation and qualification support (IQ, OQ); Amsonic is able to provide the optimal prerequisites for high quality, optimised cleaning solutions.

Fig 2: Part prior to cleaning / Part after the cleaning process.

DISCUSSION & CONCLUSIONS: Owing to the fact that system components are becoming smaller and smaller and technically more complex, the expense involved in cleaning processes is rising steadily. Meeting the today growing cleanliness demands in medical industry by using a cleaning machine as an “end of pipe” solution at the end of a production process is, at more than arguable.

Tribological Behavior of DLC Coated Spinal Disk Implants

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[2] *Synthes GmbH, Langendorf, CH.* [3] *IonBond AG, Olten, CH*

INTRODUCTION: Based on good experiences gained in many mechanical applications, diamond-like carbon coatings (DLC) are regarded as a prime candidate for protective coatings on implants. However, the body environment imposes new challenges to the layer design and requires new research into possible layer failure mechanisms.

METHODS: DLC-coated and uncoated polished ball-on-socket type implants were subjected to wear tests in a newly developed test setup simulating the appropriate body motions corresponding to in-vivo action. Data gathered included mass loss, friction coefficient, and surface roughness. The development of defects was monitored by optical microscopy, SEM/EDX, FIB cross cuts and profilometry. Additional dependencies on operational parameters (load, frequency of motion, lubricant medium) were investigated. Further data was acquired with a conventional cylinder-on-flat setup using coated samples running in synovial testing fluid (Thermo Scientific Hyclone®).

RESULTS: The DLC-on-DLC inlay pairs exhibit very low volume losses throughout the full testing cycle (corresponding to 30 years of in-vivo movement) as expected. Metal-on-metal pairs equally show low volume losses after run-in; however, it is found that the metal-on-metal pair surfaces gradually roughen in the testing process, passing into a continuous mode of high wear generation (volumetric factor of 25 vs. DLC) after 5 million motion cycles. The normalized wear values measured are comparable to published data for metal-on-metal hip joints [1]. Both surface combinations exhibit similar coefficients of friction during testing. The load vs. motion speed mappings show no difference between metal-on-metal and DLC-on-DLC for Hyclone but significant ones for non-protein media (PBS, water).

Monitoring the evolution of defects for error tolerance assessment detected the occurrence of few isolated instances which did not grow after their first appearance up to 20 million cycles (fig. 1).

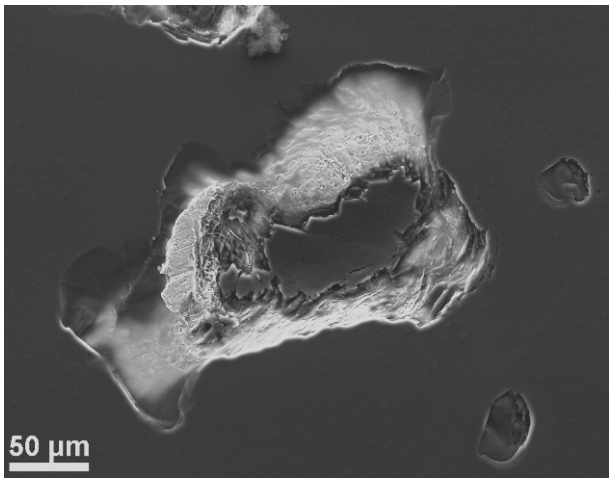

Fig. 1: Local defect on a DLC-coated implant observed after 20 million friction cycles (SEM image).

DISCUSSION & CONCLUSIONS: From the friction coefficient analyses, it is clear that the tribocontacts were operating in the mixed/liquid lubrication regimes only when triboproteins were present in the testing medium. However, there is almost no tolerance to defects (asperities, wear particles) on the metal-on-metal implant pairs, resulting in the roughening and subsequent wear observed.

The coating system presented is found to be tolerant to the detected local layer defects; however, this strongly depends on their number density and the long term interface stability, which we describe in detail elsewhere [2]. The presented coatings lead to superior performance over bare metal-on-metal counterparts.

REFERENCES: [1] J.L. Tipper, P.J. Firkins, A.A. Besong et al. (2001), *Wear* **250**:120-8. [2] C.V. Falub, U. Müller, G. Thorwarth, C. Affolter, M. Tobler, C. Voisard and R. Hauert, contribution in this volume.

ACKNOWLEDGEMENTS: Financial support from the Swiss Commission for Technology and Innovation (CTI) and Synthes is gratefully acknowledged.

UHMWPE: Effect of Gamma Radiation on the Cross Linking and Oxidative Behaviour studied with the Chemiluminescence Approach.

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INTRODUCTION: Ultra high molecular weight polyethylene (UHMWPE) is a subset of the thermoplastic polyethylene. It has extremely long chains, with molecular weight usually between 2 and 6 million. The longer chain serves to transfer load more effectively to the polymer backbone by strengthening intermolecular interactions. This results in a very tough material, with the highest impact strength of any thermoplastic presently made. It is highly resistant to corrosive chemicals, with exception of oxidizers. It has extremely low moisture absorption, has a very low coefficient of friction, is self-lubricating, and is highly resistant to abrasion. It is odourless, tasteless, and nontoxic.

Due to these properties, UHMWPE is used over 40 years as a successful biomaterial in hip, knee, and most recently for spine implants. Throughout its history, there were unsuccessful attempts to modify UHMWPE to improve its clinical performance; one attempt is the cross linking by gamma or electron beam radiation since the late 1990s.

The high energy radiation treatment leads UHMWPE susceptible to oxidative decay, due to the formation and accumulation of radical species in the polymer matrix.

METHODS: The susceptibility of UHMWPE against cross linking and oxidation was studied with the Chemiluminescence (CL) method. Degradation of hydrocarbon polymers involves a radical chain reaction, which propagates in the presence of oxygen. The CL emission mechanism arises from the phosphorescent relaxation of a triplet carbonyl species, formed in a bimolecular termination reaction by the Russell mechanism or by direct hydroperoxide decomposition. The CL-data were measured with a 1^{10} basic configuration from ACL Instruments. All samples were characterized at 37°C; after initial 24 h in nitrogen (4N), the atmosphere was switched to synthetic air for additional 24 h.

UHMWPE discs (dia 15 mm) in different variations were supplied by Dr. Lukas Eschbach, Robert Mathys Foundation RMS (Bettlach CH): not irradiated (0 Gy) and irradiated 75 - 111 kGy, each of them unstabilized and stabilized with Vitamin E.

RESULTS: The CL-data were visualized (Fig. 1) and the Total Luminescence Intensity (TLI = Integral of the CL-emission) for the nitrogen and air segment were calculated (Tab. 1).

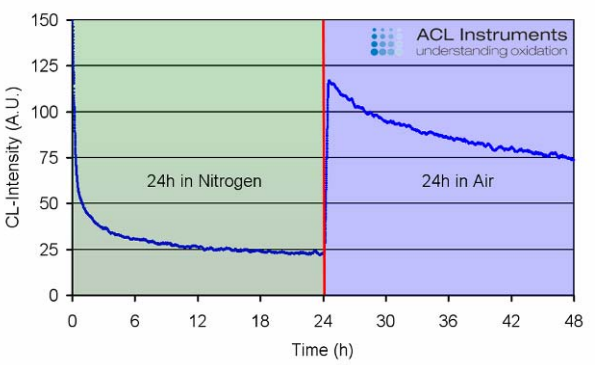

Fig. 1: CL-experiment of gamma radiation treated, Vitamin E stabilized UHMWPE: CL-emission due to cross linking in nitrogen (green part) and due to oxidation in synthetic air (blue part). The red line represents the time of switching the atmosphere from nitrogen to synthetic air.

Gamma	AO	TLI (counts)		Factor
		24h (N_2)	24h (Air)	Air vs. N_2
75..111kGy	Vit. E	209'049	641'938	3.07
0Gy	none	17'104	23'238	1.29
0Gy	Vit. E	11'314	12'656	1.12
75..111kGy	none	123'137	227'706	1.89

Table 1. Total Luminescence Intensity TLI depending on the gamma radiation treatment and the AO-stabilization.

DISCUSSION & CONCLUSIONS: The CL emission study indicates the following behaviour: Due to the gamma radiation treatment, the UHMWPE samples crosslink. This effect clearly appears in inert gas atmosphere at low temperature where the TLI is more than 10 times higher on the irradiated samples than on not irradiated samples. In the oxidising environment, the TLI values of gamma irradiated samples increase dramatically (factor higher than 25). The stabilisation of UHMWPE with Vitamin E increases the susceptibility to cross linking but also to the oxidation. On the other hand, the not irradiated, unstabilized samples are less stable against oxidation compared to the stabilized samples.

Surface Modification and Characterization of Biomaterials by Ion Beam

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INTRODUCTION: Current trends in biomaterials research are concentrated on the interactions at the implant - tissue interface and on the development of new materials with improved properties (such as biocompatibility, bioactivity and biofunctionality). These properties have to be adapted according to the function of the implant. Ion beam is an advanced tool developing and characterizing biomaterials, which allows performing both the surface-interface analyses and surface modification by implantation of ions or by irradiation [1-2]. Two case studies illustrating the applications of the ion beam in the biomedical domain are presented.

METHODS: In the first study, the surface of the titanium medical implants (screws) was modified to improve their properties (wear and corrosion resistance, bone regeneration, bone bonding, etc.). The treated implants were tested *in vivo* in the model animals (sheep). The bone/implant interface was characterized by Particle Induced X-ray Emission (PIXE) analysis. The information about bone formation and implant wear was obtained.

In the second study, the surface of some polymers (PTFE, PS) was treated with an ion beam. Polymer samples were irradiated with a 900 keV Helium beam. The irradiation lines were performed on each sample (line: 500 µm in width, 6 mm in length).

RESULTS: Case 1. Little titanium debris was observed in the bone, generally in some small blood vessels or arteries (presence of iron in bone cavity without calcium, Fig.1).

Case 2. The surface treatment of organic materials by ion beam offers several advantages: 1) the irradiation depth is well controlled; 2) the treatment could be local (through a mask) or entire; 3) surface modifications depend on the irradiation parameters; 4) the process is clean and realised in high vacuum. For the majority of the treated polymers, the cell adhesion depends on the threshold fluence (5×10^{13} at/cm^2 for a PTFE material, Fig. 2). To induce some significant modifications, which facilitate the cell adhesion on PTFE, it is necessary to multiply the irradiation dose by a factor 100 compared i.e. to the PS.

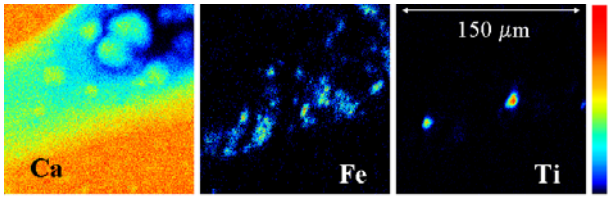

Fig. 1: Distribution of Ca, Fe and Ti in the same sheep bone area (PIXE cartographies of 150 × 150 µm^2, 2 MeV proton beam).

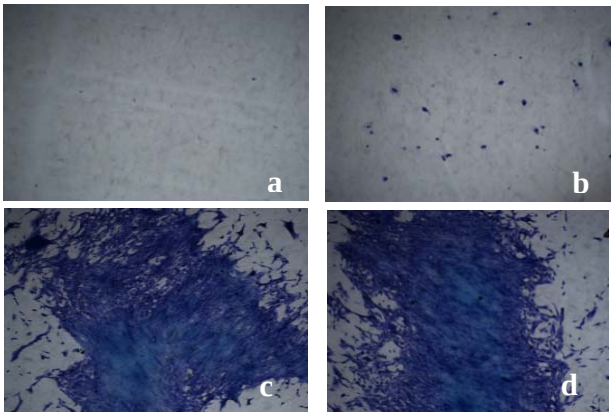

Fig.2: Optical observation of human osteoblast cell adhesion on a non- irradiated PTFE polymer (a) and irradiated at 5×10^{12} at/cm^2 (b), 5×10^{13} at/cm^2 (c) and 5×10^{14} at /cm^2 (d) fluences

DISCUSSION & CONCLUSIONS: The first study shows that due to the sensitivity and multi-element detection of the PIXE analysis, much information about the implant and the bone behaviour can be obtained. The vascularisation system and small vessels were identified in contact with the implant. It provides a possible explanation about the occurrence of Ti debris sometimes observed.

The second study shows that the surface modifications (chemical, topographical, biochemical), induced by a focused ion beam, influence the cell adhesion. The irradiation parameters (ion beam fluence, irradiation time) have to be adapted depending on the polymer material.

REFERENCES: [1] G. Guibert et al. (2008) *Nucl. Instr. and Meth.* **B 49**:813. [2] G. Guibert et al. (2008) *European Cells and Materials* **16:** suppl. 1.

Monitoring of Cellular Functions in Cells in Contact with Novel Implant-Materials

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INTRODUCTION: The development of cell based sensors as well as new material concepts for medical applications will be greatly advanced by tools that allow life-monitoring of cellular processes. For many bone-related implant concepts optimal osseointegration is generally the goal. This is facilitated by attraction of bone (precursor) cells and their maturation to bone tissue. We are establishing relevant *in vitro* systems which allow gaining information on osteo-specific cytocompatibility in tissue culture-based assays.

Properties of the cellular environment have been identified to influence cellular processes such as adhesion, proliferation, differentiation as well as extra cellular matrix (ECM) production which correlate with changes in expression of genes involved therein. Osteogenic differentiation encompasses a well organized series of events including expression of various regulatory factors. This gradual process can be followed by different marker proteins being expressed at distinct time points, comprising early and late genes. The aim of our project is to life-monitor osteogenic differentiation of cells in contact with various engineered substrates. Additionally cell-substrate interactions could be studied at the molecular level by staining or over-expression of fluorescently-tagged focal adhesion (FA) proteins (e.g. vinculin, talin).

METHODS: To allow life monitoring of osteogenic differentiation of single cells, gene constructs were created by fusing fluorescent proteins to promoters of bone specific marker proteins. Gene expression of osteogenic genes was analyzed by real-time PCR. In addition cells were immunohistochemically stained against bone-specific proteins to confirm differentiation. Furthermore, vinculin was fused to yellow fluorescent protein (YFP) by DNA cloning to visualize focal adhesions.

RESULTS: Immunohistochemical staining against bALP and collagen I show that mesenchymal stem cells can undergo osteogenesis *in vitro*. GFP expression regulated by the osteogenesis-specific promoters could be detected in osteoblastic cells. Immunohistochemical staining of vinculin and the cytoskeletal protein actin shows the morphology of cells on materials. Human fibroblasts transfected with the fluorescently-labelled vinculin show the expected accumulation of fluorescence at focal adhesion sites.

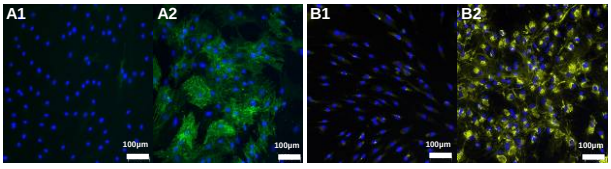

Fig. 1: ***Immunohistochemical staining against bone-specific alkaline phosphatase (bALP) and collagen 1:*** *Human bone cells were cultivated in proliferation medium (A1, B1) or differentiation medium (A2, B2) and stained against bALP (A) (green), collagen 1(B) and cell nuclei (blue) after 7 (A) or 14 days (B), respectively.*

Fig. 2: ***Live monitoring of osteogenic differentiation:*** *Schematic view of vector pOC3.8-EGFP (A1). Confocal images of immortalized MSCs transfected with pOC3.8-EGFP cultivated in proliferation (A2) or differentiation (A3) medium for 5 days.*

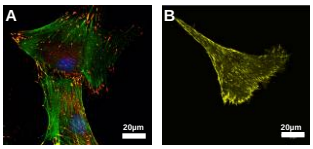

Fig. 3: ***Normal human dermal fibroblasts on novel polymer materials:*** *Cells were immunohistochemically stained for vinculin (red), actin (green) and the nuclei (blue), (A and B). Cells were transfected with gene construct pYFP-Vinculin and grown on a polyacrylamide substrate (B).*

DISCUSSION & CONCLUSIONS: Immuno-histochemical staining as well as the GFP reporter strategy allow to monitor osteogenic differentiation of cells in contact with various substrates on a single cell level. Osteogenesis could be further confirmed by real-time PCR. Cell adhesion was studied using cells transfected with YFP labelled or immunofluorescently stained vinculin.

Defining Implant Surfaces by elucidating Cell-Surface Interactions

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INTRODUCTION: A critical factor in the clinical success of an implant is the mechanisms by which it influences its surrounding biological environment. On one hand, progenitor cells contacting the implant surface are directly influenced by implant surface structure and chemistry [1-2]. On the other hand, and by selectively influencing various cell types, implant surface characteristics may impact the cell-cell interactions and competition mechanisms (cell population dynamics). As a result, a specific cell type is expected to predominantly populate the implant surface [3]. This, subsequently, will define the nature of the de-novo, peri-implant, tissue entity.

The aim of our work is to reveal the underlying processes modulating cell-surface (series 1) and cell-cell (series 2) interactions as a function of various topographical cues (i.e. structure shape, size, spatial distribution and chemistry). This is achieved by investigating the fate of human stromal, bone and fibroblastic cells as individual populations (series 1) and in co-culture (series 2).

METHODS: *Human cell culture:* Human bone marrow stromal Cells (HBMC) and bone cells (HBC) were obtained from patients undergoing hip implant surgery whilst, human skin fibroblasts (HAF) were acquired from a human biopsy. After *in vitro* expansion, fibroblasts, HBC and HBMC were cultivated in α-MEM (Invitrogen) supplemented with FCS and PSN in addition to 50 μM Ascorbic acid-phosphate, 2 mM β-glycerophosphate and 10 nM Vitamin D3. In the studies of series 1, 10 nM dexametasone was additionally added. All cultures were maintained in a humidified atmosphere, at 37° C and 5% CO_2. For experiments in series 1, HBMCs were seeded at ~ 2.5 x 10^3 cells/cm^2 and in series 2, different seeding densities of HBCs and HAFs were evaluated for cell-cell interactions. Before seeding, HBCs and HAFs were vitally labelled by Vybrant™ DiI or DiD, respectively.

Samples: Structured samples were obtained from V. Frederici and Ph. Imgrund of the IFAM in the frame of the Volkswagen Foundation project NanoMIM. For series 1 experiments at this stage, patterned grade 316L stainless steel alloy samples were produced that consisted of 30 μm diameter hemispheres and 20 μm distance between adjacent hemisphere circumferences. Plain rough (non-treated) and plane polished surfaces were produced as controls. TCPS surfaces were used at this stage for series 2 experiments.

Endpoints, cell-surface interactions: HBMC's were fixed at 24 h and day 7 in culture. The actin cytoskeleton was subsequently labelled using Phalloidin (Alexa Fluor 488, 1:40, Invitrogen). Cells were also labelled using α-vinculin mouse monoclonal IgG (clone HVIN-1, 1:300, Sigma) followed by secondary goat α-mouse IgG (Alexa Fluor 546, 1:100, Molecular Probes). Subsequently, cell architecture and attachment patterns were evaluated.

Endpoints, cell-cell interactions: Cell clustering, defined as the type (HBC or HAF) of the nearest cell, and proliferation were followed with fluorescence microscopy. Analysis was done using Visiometrics IPS and Cellprofiler software as previously described [3], at 1, 4 and 7 days.

RESULTS: Both cell attachment and cytoskeletal organisation of HBMC cells were found to be strongly affected by the micron-scale hemisphere surface arrays. The seeded cells acquired a preferential 3D conformation, characterised by increased cell height, as a function of the hemisphere structure. In HBC-HAF co-cultures, the interaction between the cells provoked a reduction in fibroblast proliferation using certain fibroblast-osteoblast ratio.

DISCUSSION & CONCLUSIONS: Our group has successfully established and implemented several methodologies to investigate cell-cell interactions and cell-surface reactions. Initial data indicates that when in co-culture, fibroblasts behaviour is influenced by the presence of osteoblasts. Additionally, the presence of micrometer-scale surface topographical features affected cell functionality, morphological conformation and motility.

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