**TRAINING SCHOOL**

**NON LIVING MATERIALS MEET LIVING BIOLOGY**

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# ABSTRACTS

## Current challenges for materials for orthopedic implants

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Abstract

In the modern era of THA, it seems that bearing surfaces (a whole chapter by itself) are the crucial issue for the long term survival of the artificial joint, and in all international hip forums, implant design and implant fixation issues are considered to have been solved. Can we therefore reply to the question, "What is the optimal design and fixation of the implant?" This question is of importance especially nowadays when Economic Health Providers are asking challenging questions.

In an attempt to throw light on the latter question, data from basic science, experimental in vivo and in vitro biological and mechanical models, autopsy specimens and long term clinical studies have been critically evaluated. It is obvious that a huge effort has been put in both by individual research centers and the implant industry without considering the cost-effectiveness of this research. It has also become apparent that theoretical and laboratory studies do not always hold up in the cold morning light of long term clinical studies and there are few quality Level I and II clinical studies. In contrast, there are numerous Level III studies in which the factors midterm follow up, patient selection criteria, one center or one surgeon experience, implant modifications and a high rate of drop out after 15 years, reveal serious defects.

## Ceramics and glasses for biomedical applications

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Abstract

Bioceramics and bioglasses are a classe of ceramic materials that are used to replace hard human tissues (bones, teeth). Due to a more and more ageing population observed since 50 years, synthetic biocompatible ceramics and glasses for bone tissue engineering gained in attention and became an alternative to natural bone substitute. The first part will give an overview of ceramic materials, with a focus on the group of structural ceramics, to which belong bioceramics. Then, bio-inert and bio-active ceramics will be further presented. Their (micro-) structure, manufacturing process, and main properties will be detailed with a conclusion about the standard materials that are today developed. The second part will be devoted to glasses, their processing and their properties by comparison with ceramics. A special attention will be paid to bioglasses, specially how they react with physiological medium.

## Metals and alloys for orthopedic and dental implants

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Abstract

This lecture addresses the processing-structure-properties-performance relationships of the commonly used metallic materials in orthopedic and dental implants, focusing on Ti-alloys (including NiTi-based), stainless steels, and CoCr alloys. The talk covers the basic metallurgy of these alloy classes, focusing on the microstructural characteristics, processing techniques, and their mechanical and physical properties. The talk also highlights some of the novel processing techniques that are increasingly being used in the manufacture of metallic implants, especially additive manufacturing.

## Bone Cements and Substitutes – the Advantages and Limitations of Ceramics

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Abstract

Fixation of bone and of orthopaedic devices and bone substitution present many challenges to the materials scientist, particularly those that are required to take up the physical form of a defect in bone and react to form a substitute of cement in situ. The scope of fixation and substitution strategies will be discussed and those materials currently approved for clinical use will be critically reviewed. The deficiencies of current materials will be discussed in terms of the relationships between material properties and their clinical performance, as well as the consequent implications for areas of future development. The potential of ceramic and/glass based materials will be discussed in this context.

## Bone: structure and properties, cell biology, bone physiology

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Abstract

Bone is a hard tissue which is responsible of the different posture of live animal and of their mobility. Several cells are involved in bone formation, growth and maintenance. However, osteoblasts and osteocytes are the main two cells types accountable for bone formation and bone resorption, respectively. Other cells types and tissues are also involved in the overall bone health. First at all, blood vessels (no bone without blood), nerves, cartilage (fundamental for friction less movement), endosteum, periosteum and finally the bone marrow tissue, the source of hemopoietic and mesenchymal stem cells. Bone is not only a structural tissue but many essential biological processes involved bone, such calcium and phosphorus homeostasis, growth factors (TGF beta, BMPs, IGF, etc.) and fat storages as well as endocrine functions. Today, with increasing human life expectancy, bone tissue is under pressure and plays many important roles in several clinical conditions, such osteoporosis, implant stability and integration or implant looseness, with major clinical consequences. An overview of these different bone physiology and pathophysiology aspects will be discussed.

## Bio-interfaces and their dynamic evolution

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Abstract

A bio-interface is any interface between a biological molecule and an organic/inorganic material. The simplest bio-interface is created when a biomolecule such as RNA, DNA, protein, antibody etc. touches a solid surface. Complex bio-interfaces include larger biological entities such as membranes, viruses and cells that are brought into contact with organic/inorganic materials or synthetic man made materials.

In this seminar, biological examples will be used to explain the role of bio-interfaces on the behaviour of natural materials (e.g., mechanical properties) as well as biological properties. Other examples will include synthetic materials e.g., bioactive materials that form a chemical bond with natural tissues e.g., bone forming a powerful bio-interface that controls tissue growth and regeneration.

## In vivo experimental procedures

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Abstract

It is important to test tissue engineering approaches before they are transferred to the clinical arena. This testing is first performed in vitro. However, in vivo studies are necessary and demanded by federal institutions. The studies have to be performed according to animal welfare guidelines causing as least suffering as possible for the experimental animals involved. Special notice needs to be given to the 3R's principle.

Depending on the subject area of interest, different models have to be applied. For bone regeneration, for instance, it has to be determined whether you want to perform a functional or a mechanistic study. Furthermore, is the bone of interest subjected to load-bearing or not. This is related also to maxillofacial or trauma-orthopaedic applications. The answers to these questions partially determine the species to be used. This is also related to small and large animal models. Typically, one starts with a small animal screening model, then going to a more clinically relevant small animal model. Final tests should be performed in clinically relevant large animal models. An example of a series can be as follows:

First, a simple drill hole model in the femur of rats is applicable for screening purposes. Having assessed the best concentration etc. the cells or drug can be applied in an non-union femur defect model in the rat. In the last phase, a sheep segmental defect model in the tibia can be used. An intramedullary nail is inserted and locked in the tibia. A 2.5 cm segment is excised causing a non-union defect. The defect can be filled with substances and healing can be assessed by µCT and histology.

It is important to choose the optimal animal model for the hypothesis tested. It is also important to use sophisticated methods to obtain good quality data. Furthermore, one should have experience in applying the animal models to obtain consistent and reliable data.

## Scaffold design, processing, biodegradation & resorption

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Abstract

The research in bone tissue engineering is nowadays mainly focused on the development of alternatives to autologous bone grafts for bone reconstruction. In this tutorial lecture, various techniques to manufacture bone substitutes in bioceramics and biopolymers will be largely described. The physical and mechanical characteristics of the various as-obtained scaffolds will be compared and the impact of the porous architecture and the material composition on the cell proliferation and differentiation will be discussed.

## Mechanobiology: may the force be with you

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Abstract

Cellular migration, division or proliferation are highly dynamic biological processes that are essential to the development of an organism (morphogenesis), wound healing, cancer metastasis or immune response. A cell spreading on a natural or synthetic matrix experiences various external forces, which include resistance from the surrounding medium, cell-substrate interaction forces, and internal forces that are generated by the cytoskeleton. A basic question we must address is to understand the mechanisms used by cells to sense mechanical signals and transduce them in intracellular biochemistry and gene expression - a process that is known as mechanotransduction. To answer this question, important efforts have been directed during the last decades towards understanding the role of physico-chemical properties of cell matrices, such as the ligand species, lateral density and distribution of active sites, mechanical properties and micrometer- or nanometer-scale topography. During this course, I will describe some impressive progresses that have been made on the way cells respond dynamically to substrate properties, with an emphasis on the physical basis of the forces that govern the behavior of migrating cells.

## Bone Tissue Engineering, current trends

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### Abstract

Bone tissue engineering (BTE) has been proposed as an alternative treatment to autogenous cancellous bone grafts for the restoration of bone tissue loss. Up to date, typical BTE constructs have combined three main elements to achieve successful bone formation: progenitor cells for osteogenesis, growth factors and other matrix proteins for osteo-induction, and an osteo-conductive scaffold to provide a framework for host tissue ingrowth and act as a carrier for implanted cells and/or inductive agents. Osteo-conduction requires high porosity in order to facilitate high surface area for cell-scaffold interactions and sufficient space for extracellular matrix (ECM) deposition. The pore structure must be interconnected to provide adequate permeation of nutrients and removal of cellular waste both in vitro and in vivo, as well as to permit neovascularization from the host site. Ideally, the scaffold should degrade or be remodeled as bone regenerates. Adult stem cells have been the most utilised osteogenic elements due to their high proliferative and osteogenic potential, as well as their relatively easier harvest. The choice of osteo-inductive agents has been controversial, as several of the growth factors are suspected of carcinogenic potential.

Although BTE has been investigated for several decades, it has still not fulfilled its promised potential in clinic. Bone is an inherently complex and dynamic form of mineralized collagenous tissue that remodels throughout life to adapt to mechanical stress, and maintain ionic balance and skeletal tissue integrity. The biggest challenge of BTE has been the lack of hierarchical microstructure that can adapt to the dynamic in vivo environment, and the vascular supply that is required for the high demand of O2 and nutrients through this adaptation.

Current trends to accelerate utilisation of BTE products in clinical environments has been focused on five main approaches:

1. Bioinspired scaffold fabrication techniques, that include integration of hierarchical micro- and nanostructures of natural bone into single scaffold structure, together with template modulated biomineralisation;
2. Injectable polymeric or peptide hydrogel systems that offer less invasive and more conformable filling of the defect area;
3. Pre-vascularisation strategies with co-culture systems using endothelial cells and vascular networks within the BTE constructs;
4. Bioreactor systems that mimic the mechano-environment of bone in order to stimulate natural bone growth as well as to accommodate larger scaffold sizes;
5. Utilisation of induced pluripotent stem (IPS) cells and other gene therapy approaches for reduction of immune system reactions and improved osteo-induction.

Combination of two or more of these approaches may hold promise for production of more clinically relevant, vascularised and functional BTE constructs with high shape complexities, and possibly patient- and/or defect specific implants.

# Biocompatibility in the scope of Bone Engineering: Definitions and Standard Process and Testing

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## Abstract

Term "biocompatible" implicates some expectations regarding the properties of a biomaterial or a medical device. It must clarified that this term is used differently in academic research as compared to industrial settings or regulatory purposes. Historically, biomaterials and medical devices have been designed initially to be as inert as possible, but modern medical devices interact with the host, which requires some form of biological functionality.

In the past year's more than 30'000 papers have been published by academic research groups on scaffolds and devices for tissue engineering purposes. When reading the current literature, it is evident that author's conclusions were generally speaking always positive with regard to their materials, i.e. that their scaffold materials were superior or that it exerted the anticipated effect. Unfortunately, these results can typically be not compared to other publications since either carful characterization of raw materials and finished materials or the scaffolds was omitted, or the tests were done based on established in-house protocols that differentiate between each other in fundamental aspects. The lack of comparison is one of the major reasons that such results are used by industries. From an industrial point of view, characterization is based on paradigms that have been set some 30 years ago. General procedures are outlined in medical device regulations. Details are described in internationally recognized standard guidelines and standard test methods. Thus, biocompatibility of medical devices has to be proven according to those standards. The main purpose of the testing is to reduce the risk for the patients and to guarantee for equal treatment of the companies in the approval process. Criteria are described that define whether a test is passed or failed.

It is the aim of the lecture to describe the general process for establishing biocompatibility according to ISO 10993-1 and its associated standard test methods. It includes testing regarding chemical and physical properties as well as in vitro and in vivo performance. Furthermore, current attempts in characterization of tissue engineered medical products (TEMPs) are briefly discussed.

# Tissue Engineering in Orthopedic Sports Medicine: Current Concepts, Surgical Aspects and Future Directions

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## Abstract

The field of orthopedics has a long history of embracing new technologies. From total joint replacement to the use of recombinant human bone morphogenetic protein-2 orthopedic surgeons and biomedical engineers are working hard to create novel strategies to repair and/or replace damaged tissues. Tissue engineering has been revolutionizing the concepts and therapeutic approaches for the treatment of different sports injuries. To overcome the drawbacks of the current treatments, tissue engineering (TE) based strategies provided new possibilities, either in the treatment of defects, which were previously considered unrecoverable, but also in what concerns to the decrease of recovery time. Supported in three mainstream concepts, TE uses the combination of scaffolds, cells and biological factors to pursue a better functional regenerative process. However, it is important to understand that there is still a long way to go until these new approaches turn out to clinical practice.

This review aims to overview the current concepts of tissue engineering applications in orthopedic sports medicine in animal and clinical research applied to growth factors, scaffolds and stem cells.