Adaptable dentistry

Professor Christine Knabe-Ducheyne offers some details into her work researching new materials for dental bone augmentation which can be tailored for specific clinical applications

With regards to implants, how have clinical areas such as dentistry and orthopaedics evolved?

There has been a significant increase in dental implants and in alveolar ridge augmentation procedures, which has led to an ever-increasing demand for adequate bone grafting materials. In addition, with the increased use of osseointegrated dental implants and with many implants functioning for a long time, the treatment of peri-implant bone loss due to infection has gained increasing importance.

Although autogenous bone grafts are currently the standard of care, bone substitute materials are extensively studied in order to avoid harvesting autogenous bone. As a result, there has been heightened demand and an ongoing search for synthetic, biodegradable bone substitute materials that facilitate bone repair and replacement by fully functional bone tissue.

Which smart biomaterials are you investigating in particular, and what makes them so advantageous towards bone regeneration?

Our research focuses on interdisciplinary translational research regarding smart bioactive resorbable calcium alkali phosphate-based biomaterials for bone regeneration and bone tissue engineering applications. These materials have a greater stimulatory effect on bone cell differentiation and bone tissue formation compared to clinically established bone grafting materials, in combination with a higher biodegradability. Contact of these materials with body fluids leads to surface transformation events involving dissolution and reprecipitation which lead to silicon release, calcium uptake and protein adsorption. Bone cells adhere to these transformed surfaces via specific cell surface receptors and as a result they facilitate faster bone regeneration and repair.

Are you currently using any unique methods to gather your research? Could you briefly discuss your team's use of computer tomography in relation to bone formation?

We currently develop therapeutic strategies which facilitate bone tissue engineering of large segmental defects. It involves fabricating 3D structures of these calcium alkali phosphate materials by 3D printing. We then also use mesenchymal stem cells and microvascular techniques for adequate blood vessel formation. We utilise a perfusion bioreactor to cultivate mesenchymal stem cells within these scaffolds prior to implanting them into large segmental defects in laboratory animals in order to achieve bone repair of these defects, which typically are extremely difficult to repair.

In separate studies, synchrotron-based microcomputer tomography has facilitated 3D visualisation and volumetric analysis of the newly formed bone tissue as well as of the degrading bioceramics in biopsies harvested from patients at dental implant placement six months after sinus floor augmentation with tricalcium phosphate and in specimens harvested from sheep, at a very high resolution of below 1 μm.

How are you looking to disseminate your research results and what applications are you hoping your findings will have?

We are disseminating our research results by presenting them at international scientific meetings and publishing them in the leading journals of the biomaterials field and respective textbooks including *Comprehensive Biomaterials*, a major reference work covering all major aspects of biomaterials research. We hope that our findings will contribute to providing a range of smart bioactive bone grafting materials and therapeutic strategies for patient care, materials which are optimally tailored for various clinical applications and whose efficacy has been proven in an evidenced-based manner.

Are you looking to focus your research efforts elsewhere in the near future?

An important component of our research increasingly involves bioactive sol-gel based materials, which feature controlled and

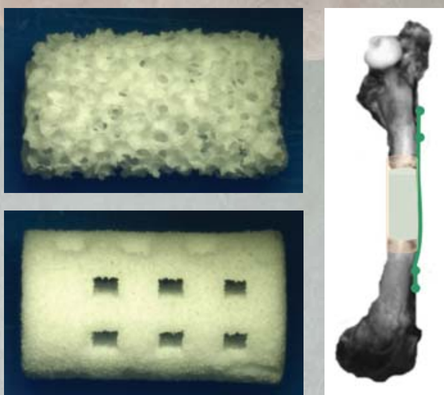


FIGURE 1. 3D-CALCIUM ALKALI PHOSPHATE SCAFFOLDS FOR BONE TISSUE ENGINEERING

tailored release of various molecules such as antibiotics and factors that inhibit bone resorbing cells, namely osteoclasts. These materials are designed and specifically tailored to treat chronic inflammatory bone loss conditions resulting from infections which are hard to eradicate. This addresses a number of clinical conditions for which therapies with predictable success rates do not exist such as refractory infrabony defects in periodontitis, periimplantitis, osteomyelitis, periprosthetic infections and prevention thereof. In this context we deal with interdisciplinary research involving the fields of implant dentistry, craniofacial bone regeneration, periodontology, orthopaedics and traumatology.

Would you like to discuss any other aspects of your work?

We are also studying the effect of gender, age and hormone status on bone formation after sinus floor augmentation with tricalcium phosphate with the goal of identifying parameters which can be used as predictive tools for indicating how fast bone regeneration will proceed in a given patient. This will help with determining the ideal time for re-entering the site and placing the dental implants, and is an effort towards creating personalised medicine.

Smarter bioceramics

Work is currently underway at **Philipps-Universität Marburg** in Germany to develop smart, rapidly resorbable bioceramics for bone regeneration in regenerative medicine and implant dentistry

THE USE OF oral implants has become a common treatment to replace missing or lost teeth. However, when teeth are missing, the surrounding bone and soft tissue can break down as a result of the natural resorptive process. This creates a condition that must be treated, since the requirements for the design of implant superstructures, rather than the bone volume available, dictate the position in which the dental implants have to be placed. Thus, the resorption of the alveolar ridge after tooth extraction oftentimes necessitates that the site is developed by bone and soft tissue augmentation before implant placement. In orthopedics, 80 per cent of fractures that are treated with osteosynthetic materials require adjuvant grafting in the US.

Currently, autogenous bone grafts are mostly used for bone reconstruction in orthopedics and cranio-maxillofacial surgery. Bone is harvested from a donor site located in a different area of the patient's body. Among the various techniques to reconstruct or enlarge a deficient alveolar ridge, guided bone regeneration (GBR) and sinus floor augmentation procedures have become well-established surgical approaches. Autogenous bone grafts are usually combined with barrier membranes. These autografts have been used to reduce the defect volume, thereby stabilising the blood clot, and to support the membrane as a space-maintaining device, thus preventing their collapse into large defects.

BONE SUBSTITUTES

The use of autogenous bone, however, has several disadvantages: the need for an additional surgical site, donor site morbidity exceeding that at the treatment site, insufficient volume of harvested bone, and the need for general anaesthesia to harvest extraoral bone. These problems have led to extensive research into bone substitute materials. Professor Christine Knabe-Ducheyne from the Philipps-Universität Marburg, Germany, is leading a team of researchers who are investigating the use of smart, rapidly resorbable bioceramics for use in regenerative medicine and implant dentistry.

"Among alternative graft choices, synthetic bone substitutes are superior to freeze-dried human allografts or bovine-deproteinised bone xenografts in several respects," Knabe-Ducheyne explains. "They excel in terms of safety profile, as there is no risk of disease transmission or immunological challenges." The ability to bond to bone tissue and stimulate bone formation at their surface is a unique property of bioactive ceramics. They are used as bone grafting materials and as coatings for titanium and its alloy. These coatings have been shown to accelerate initial stabilisation of implants by enhancing bony ingrowth and stimulating osseous apposition to the implant surface, thereby promoting a rapid fixation of the devices to the skeleton.

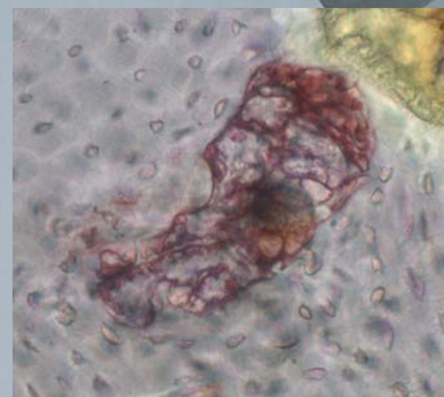


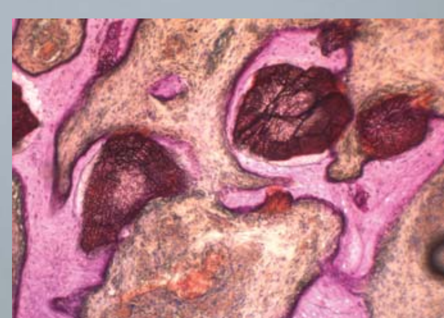
FIGURE 2. HISTOMICROGRAPH OF NEWLY FORMED BONE AND DEGRADING CALCIUM ALKALI PHOSPHATE GRANULE.

BIOACTIVE CERAMICS

Numerous bone grafting materials have been developed and studied since the late 1970s. The majority of these grafting materials are calcium phosphate-based materials. The bioactive ceramics most commonly investigated for use in bone regeneration are β-tricalcium phosphate (β-TCP), hydroxyapatite (HA), and bioactive glasses such as bioactive glass 45S5 (BG45S5). All of these materials are biocompatible and osteoconductive. However, they differ considerably in the rate of resorption.

A biomaterial used as a bone substitute should be a temporary material serving as a scaffold for bone remodelling. The material must degrade in a controlled fashion into nontoxic products that the body can metabolise or excrete via normal physiological mechanisms. Moreover, this substance should be resorbable and should

FIGURE 3. HISTOMICROGRAPH OF CALCIUM ALKALI PHOSPHATE INDUCING NEW BONE FORMATION AT ITS SURFACE



THE EFFECT OF RAPIDLY RESORBABLE, BIOACTIVE BONE SUBSTITUTE MATERIALS ON OSTEOBLASTIC CELL DIFFERENTIATION

OBJECTIVES

The objective is to optimise smart bioactive bone grafting materials, which possess the intrinsic capability to stimulate bone cell function and bone formation. This further entails optimising bone engineering and therapeutic concepts for bone regeneration primarily in the context of implant dentistry and orthopaedics with a focus on translation.

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undergo complete remodelling and substitution by newly formed functional bone tissue. While some HAs display excellent osteoconductive properties, they also exhibit limited biodegradability. Other HAs show varying degrees of osteoconductivity and bone-bonding behaviour. Both TCP ceramics and BG45S5 have been shown to possess excellent osteoconductivity, bone-regenerative capacity, and bone bonding behaviour in combination with a higher biodegradability than various HAs.

Compared to the bone substitute materials which are currently clinically available, there is a significant need for bone grafting materials that degrade more rapidly, but at the same time stimulate osteogenesis. As a result, considerable efforts have been undertaken to produce rapidly resorbable bone grafting materials that exhibit good bone-bonding behaviour by stimulating enhanced bone formation at the interface in combination with a high degradation rate.

CALCIUM ALKALI ORTHOPHOSPHATES

This need has led Knabe-Ducheyne's team to examine a series of bioactive, rapidly resorbable glassy crystalline calcium alkali orthophosphate materials. These materials have a higher solubility than TCP and therefore they exhibit a higher degree of biodegradability. On this basis, they are considered as excellent candidate materials for alveolar ridge augmentation. Furthermore, various calcium phosphate materials with addition of silicon have been developed with the intent to enhance their bioactivity and mechanical stability.

Recent studies performed by the team have provided insights into the effect of various bioactive ceramics on bone cell differentiation and tissue maturation *in vivo*, thereby allowing for correlation of *in vitro* and *in vivo* events. The researchers first established an *in vitro* cell culture assay, by which they were able to demonstrate the greater stimulatory effect of certain calcium alkali orthophosphates compared to clinically used bone grafting materials. They then established the correlation between *in vitro* and *in vivo* events by showing that these materials induced greater and more expeditious bone tissue maturation and formation in a clinically relevant animal model. Hence, these materials facilitated excellent bone regeneration in combination with a high biodegradability resulting in substitution by fully functional bone tissue.

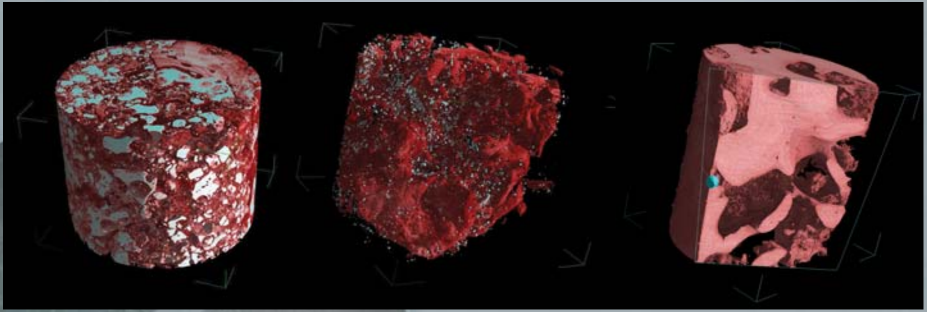
DEVELOPING TAILORED CLINICAL APPLICATIONS

The researchers have focused their efforts on understanding the underlying mechanisms by which bioactive ceramics stimulate bone tissue formation. Attention has been directed toward the atomic and molecular phenomena occurring at the material surface and their effects on the reaction and signalling pathways of cells and tissues. Once reaction pathways are clearly identified, the means have become available to alter biomaterial molecular components and surface characteristics in ways that promote more expeditious and enhanced bone formation in combination with a desirable biodegradability, and thus, to create bioactive calcium ceramics and glasses that are optimally tailored toward their clinical application.

The team has already developed such smart bioactive calcium alkali orthophosphate materials which stimulate bone cell function and bone formation: "Their composition and surface properties are optimised in such a fashion that they exhibit an optimal stimulatory effect on bone forming cells and counter events which lead to bone loss," Knabe-Ducheyne elucidates. "This includes bone grafting materials in the form of granules, as well as self-setting injectable or mouldable putty-like bone substitute cements which are advantageous for restoring outer contours. This is in addition to 3D structures fabricated from these materials by 3D printing for bone tissue engineering applications." The calcium alkali phosphate based bone substitute granules have received a CE mark, are commercially available, and thus, have been successfully implemented into the clinical arena.

The researchers are now aiming to take several more of these smart bioactive biomaterials and therapeutic concepts to the clinical arena by following a pathway including in vitro cell culture studies, preclinical in vivo animal studies and controlled clinical studies in a dually evidence-based fashion. Knabe-Ducheyne explains this approach: "First, we aim to understand the molecular mechanisms by which these materials interact with cells and tissues and enhance osteogenesis. And second, we focus on demonstrating the superiority of these novel optimised materials and therapeutic approaches compared to clinically established materials by providing long-term data of controlled clinical trials".

FIGURE 4. SYNCHROTON-CT IMAGES OF BIOPSIES HARVESTED AFTER SINUS FLOOR AUGMENTATION WITH TCP



Philipps Universität Marburg