Repair and regenerate

Professor Ståle Petter Lyngstadaas profiles the University of Oslo's Department of Biomaterials

THE FOCUS

Our research focuses on the development and modification of biomaterials for skeletal repair and regeneration, and the engineering of bone, teeth and cartilage tissues. This encompasses several strands:

- Developing bioactive surfaces for implants and bone graft substitutes
- Studying the role of the extracellular matrix, intrinsically disordered proteins and focal adhesion mechanisms in healing, regeneration, mineralisation and implant integration in skeletal tissues
- Providing clinically- and industrially-applicable surfaces optimised for stem cell recruitment and growth for use in bone-anchored implants and bone graft substitutes

WHO WE ARE

The research team includes researchers trained in materials science, chemistry, physics, medicine, dentistry, veterinary medicine, biochemistry, molecular biology and technical design. A multidisciplinary team with a wide network comprising both users and manufacturers is absolutely crucial to maintain control over each stage of research and ensure our solutions are biologically, clinically and commercially sound. We aim to oversee materials from bench to bedside: we believe a holistic view is essential for understanding how the body interacts with foreign materials, and how we can manipulate and manufacture the materials to work better within the body.

RESEARCH SNAPSHOT

We designed, developed and refined a titanium oxide ceramic for use as a synthetic bone graft material. This involved several stages, including chemical surface modification, physical and chemical testing of key properties in cell cultures and small animals, redefining process parameters, and designing the production process. We then set up a production line to evaluate variability between batches and the effects of storage. The final stages involved defining a method for sterilisation, employing a large animal model and, lastly, clinical testing in patients.

NURTURING TOP TALENT

Currently, we have 16 PhD candidates from nine countries, representing a diverse range of academic backgrounds. The PhD students not only teach in the traditional way, but function as supervisors for graduate students who in turn would like to run research projects. This provides a great experience for all involved.

Moreover, the proximity to clinical research allows the young researchers to see their own inquiries as part of the whole picture, which enables a fuller appreciation of their own projects and application-driven research.

PATENT AND PERTINENT

Our patent portfolio covers new materials and devices for treating severe loss of skeletal tissue. Treatments for these ailments currently come up short in terms of restoring both form and function.

The new materials and devices we have developed are incremental steps towards the 'perfect' materials which, we hope, will work seamlessly with the body to recreate what was lost to disease or trauma.

ACHIEVEMENTS

Among the group's major achievements is the identification and utilisation of molecules previously unknown to bone biologists, such as ameloblastin and leptin. We have also excelled in making better surfaces for bone-anchored implants – which are now in clinical use worldwide – as well as making a big contribution to the understanding of the effect of roughness on bone growth. Additionally, we have contributed significantly to the development of bone graft substitutes and to the understanding of adverse reactions in peri-implant tissues. Finally, we have studied the molecular basis of several diseases involving bone-cell signalling and the interaction between cells, as well as the extracellular matrix during skeletal growth and mineralisation.

Finding the matrix

Nano-based treatments that will help to reduce healing time for wounds

THE FIELD OF biomaterials covers all devices and materials that interact with biological systems, though is most commonly associated with implants and transplants. Materials employed can be organic, such as human or animal cells, or synthetic, such as metallic or ceramic devices. A major focus for the field is improving how efficiently the body is able to adopt these new materials.

Headed by Professor Ståle Petter Lyngstadaas, the Department of Biomaterials at the University of Oslo adopts a specific focus on bone and cartilage tissue. The Department takes advantage of its situation within the university's Institute of Clinical Dentistry, orientating much of its research towards dental knowledge and applications.

The faculty contains one of northern Europe's largest dental clinics, which treats more than 50,000 patients every year. This proximity between clinic and lab provides several benefits, as Lyngstadaas observes: "Our collaborations have created a fantastic environment for testing new ideas and materials; they ensure that the clinic is research-orientated and provide our laboratory with first-hand experience and feedback from the use of biomaterials". Thus, a reciprocal, mutually beneficial relationship has been fostered, making it possible to train dental specialists in the properties and applications of advanced biomaterials.

Lyngstadaas considers this access to first-hand experience to be one of the Department's major strengths, as it provides researchers with the capacity to see the transition of biomaterials from the lab bench through to clinical application. This holistic approach enables the research groups to be involved in each stage of development: "We are able to produce and design biomaterials, test their material science properties, study *in vitro* performance, research these materials in various animal models and study their performance in humans," Lyngstadaas surmises. Indeed, the Department of Biomaterials brings together a range of disciplines and specialisms, ensuring the researchers have access to and understanding of each phase of research and development.

HARD TISSUE, CONCRETE GOALS

In 2002, the Department undertook the project, Stable extracellular matrices as novel biotherapeutics for biomimetic induction of hard tissue growth. Backed by a grant of €2.8 million, it was the largest EU-funded project to run at the University of Oslo at that time.

The project aimed to induce hard tissue healing and regrowth through biological means. This involved isolating and testing extracellular matrices from porcine samples and clones from human cDNA libraries. The goal was to isolate at least one stable, bone-inducing macromolecule. After evaluating 72 hard tissue matrix fractions, the project identified four extracellular matrix fractions that have promising bioactivity. These fractions were subjected to expanded biological assays to gauge their growth characteristics, dose-response relationships and adhesion to biological and titanium surfaces.

Focused on developing a workable treatment with a biological basis, the project aimed towards reducing reliance on synthetic materials for implantation. This development has huge clinical advantages, impacting greatly on the care of patients suffering from diseases or traumas affecting skeletal tissues. Specifically, induction of hard tissue regrowth can reduce the loss of important tissues and thereby lessen the need for subsequent repair by prosthetics, resulting in reduced healing time and less discomfort for the patient.

In dental applications, inducing hard tissue growth can restore the infection barrier and thereby contribute to the prevention of cardiovascular diseases. This is a major pathway to improve the health and quality of life of the ageing population. Furthermore, the research has boosted the Department's international profile, and helped to develop the researchers' network across the EU. A public website has been launched and is updated frequently (see Intelligence).

AN ALTERNATIVE TREATMENT

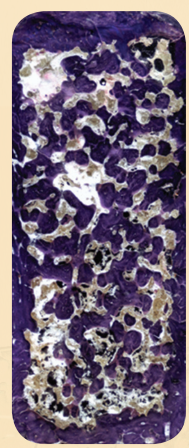
Where the treatment of wounds is concerned, the likelihood of infection is minimised by the use of topical antimicrobial agents. These are typically antiseptic agents, such as iodine and silver, and antibiotics.

Through the looking glass

The Department of Biomaterials benefits from advanced laboratory facilities, enabling:

- Production of polymers and ceramic materials
- Chemical modification of surfaces by ion implementation
- Nano-scale observations through advanced imaging systems

The researchers are experienced in the use of animal models, having conducted studies of bone healing and implant performance in rats, rabbits and pigs, and extending them to clinical trials in human groups.



Left: Titanium dioxide scaffold can be made to any shape. The material is easily drillable for placement of dental implants.
Right: Newly formed bone trabeculae were found throughout the scaffold volume after six weeks of healing in minipig jaw.

The silver ion is the most common topical agent in the care of burn wounds. However, to date, it has not been able to provide affirmative results and remains costly to manufacture. In addition, silver cannot be used on patients with acute sensitivity to the metal; nor can it be used during radiation treatment or X-ray examinations.

Another option for wound dressings is to use titanium dioxide particles. Recent research into the utilisation of these particles has centred on activating them by exposure to UV light. The Department of Biomaterials has developed an alternative method of activating the particles by exposing them to hydrogen peroxide. This has helped to make titanium dioxide a viable choice, which is cheaper and more biocompatible than current alternatives.

When introduced into a wound, the activated titanium oxide particle will specifically destroy the membrane of bacterial cells without harming the body's own cells, which are inherently resistant to their action. Once it has fulfilled this function, the particle will return to its natural and safe state; it can then be easily removed and dissolved by the body's immune system without any harmful effect.

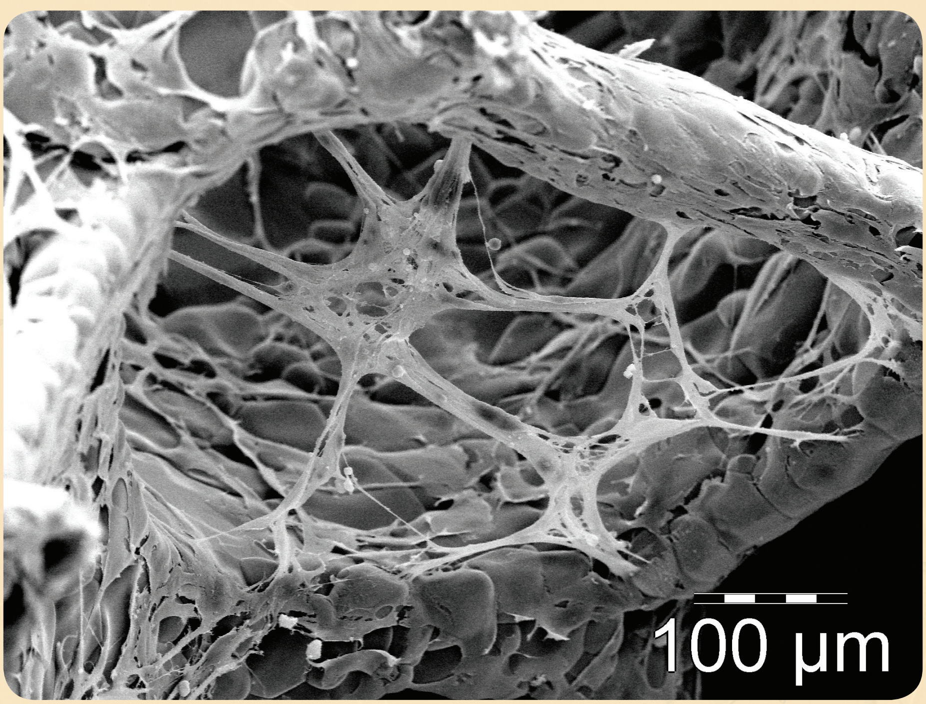
The advantage of this approach is that there is no need for antibiotics. The use of antibiotics is currently reduced in healthcare due to the prevalence of multiple-drug-resistant bacteria, commonly referred to as superbugs. As titanium dioxide is not drug based, bacteria is much less prone to develop or inherit resistance to it. As such, it can be used widely for long periods.

Highly interdisciplinary

The design and development of a medical device or biomaterial involves contributions from a range of medical and scientific specialisms. Materials are designed and evaluated in terms of composition (**chemistry**), strength (**physics**), and biological response (**biochemistry**, **molecular** and **cell biology**); and tested in animal models (**veterinary medicine**) and clinical trials (**medicine** and **dentistry**).

INDUSTRY PARTNERSHIPS

The Department has built strong relationships with several SMEs and major players in the fields of implants and wound care. Lyngstadaas describes these partnerships as valuable for benchmarking the Department's approaches against the needs of the market and population: "If our approaches don't match these needs, the ideas will never be brought into clinical use and our efforts will have been mostly wasted, aside from the benefits of generating knowledge and experience, of course". As such, the Department strives to design approaches that industry can develop into commercial products. Industry partners are therefore crucial in terms of offering design input, helping to make the materials suitable for development.



OSTEOBLASTS INSIDE A TITANIUM DIOXIDE SCAFFOLD

INTELLIGENCE

DEPARTMENT OF BIOMATERIALS, UNIVERSITY OF OSLO

OBJECTIVES

- Develop bioactive biomaterial surfaces through modification of micro and nano structure, and by ion implantation and biomolecular coating of the biomaterial surface layer
- Study the role of focal adhesion mechanisms in implant performance
- Study the role of intrinsically disordered proteins in surface recognition and biomineralisation
- Study the biology of compromised bone during healing and implant integration
- Develop implant surfaces that provide a focal adhesion contact for cells in the peri-implant environment

CLOSEST INDUSTRIAL PARTNERS

Corticalis AS, Norway • **Institut Straumann AG**, Switzerland • **Mölnlycke Healthcare AB**, Sweden • **Numat Biomedical SL**, Spain • **SINTEF**, Norway • **Tigran Technologies AB**, Sweden • **TiKoMed AB**, Sweden • **Tokushinkai Group**, Japan • **KEY**

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