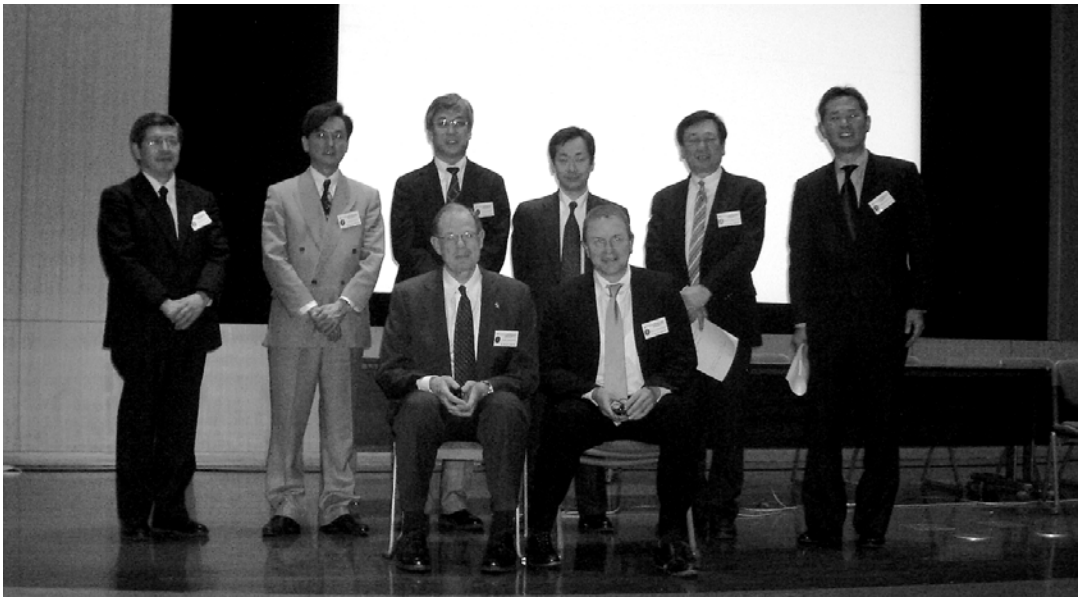
21st Century Center of Excellence (COE) Program for "Frontier Research Program on Molecular Destruction and Reconstruction of Tooth and Bone"

The 12th Symposium

Recent Advancement of Dental Implant Treatment: Fusion with Regenerative Medicine

January 20, 2008 National Center of Sciences



Program

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11:25 - 11:45	Shohei KASUGAI		New Bone Substitute for Dental Implant Treatment: Combination with -TCP and Simvastatin
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13:00 - 13:50	Rainer SCHMELZEISEN		Chair Side Stem Cell Application in Dentistry and Implantology
13:50 - 14:30	*Hideaki KAGAMI*		Tissue engineering of oral and maxillofacial tissues using somatic stem cells : Safety and efficacy of bone regeneration therapy using mesenchymal stem cells at the Institute of Medical Science Research Hospital: A preliminary report
14:30 - 15:10	Yuichi IZUMI		Periodontal Tissue Regeneration at Present and in the Near Future
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9:30 – 9:40

Masaki NODA
Leader of 21st Century of Excellence (COE) Program for “Frontier Research Program on Molecular Destruction and Reconstruction of Tooth and Bone”
Professor of Molecular Pharmacology, Medical Institute, Tokyo Medical and Dental University

Introduction

Currently, the longevity of life in Japanese nation has been tremendously increased and it is expected that this trend will further continue for the future. With such long life time expectancy, it is important to preserve the mastification function for the maintenance of high quality of life. Implant treatment provides efficient recovery of mastification function in the individuals who have lost their own teeth. It is important that the patients could avoid the issues and problems associated with prosthesis. Design of implants, procedures to set the implants and maintenance of the implants are major issues to bring ideal outcome of this treatment. To enable the setting of the implants properly, the patients need to maintain certain levels of bone mass in their jaws. If the period of loss of teeth prolonged, bone levels in the jaw will reduce significantly. Therefore, in order to establish efficient and the safe implant treatment, it is required to preserve the levels of bone. Therefore, regeneration medicine for the jaw bone is another issue which is requiring the current technologies of the bone-related medicine. This symposium will focus on the implant treatment as well as the recovery of bone mass utilizing the regeneration measures. It is our honor and privilege that world-top class investigators in this research area are participating in this conference. The topics to be discussed in this International Symposium of the 21st Century Center of Excellence(COE) Program will provide us most updated information to further step up the implant and regeneration treatment.

9:40 – 9:55

Shohei KASUGAI
Prof. of Oral Implantology and Regenerative Dental Medicine, Graduate School, Tokyo Medical and Dental University

Fusion of Dental Implant Treatment and Regenerative Treatment

Loss of teeth does not threaten the patient's life; however it decreases quality of life of the patient. Dentists have been treating edentulous patients with prostheses from ancient times. The finding of "osseointegration" by Dr. Branemark is a breakthrough in dentistry and since then, modern dental implant treatment started. It has been widely accepted that dental implant treatment with titanium screw type implants is predictable and recent advancement of dental implant treatment is really remarkable. We can provide patients highly esthetical and functional outcome with less pain in short period. However, this kind of treatment is possible only in a favorable case in which a patient has enough bone and soft tissue at the implant installation site. Notably, dental implant is an artificial organ, which replaces lost or malfunctioned part of the body.

Tissue engineering is a new field of sciences, the final goal of which is regenerative treatment. Obviously, instead of replacing lost or malfunctioned part of the body with materials, regeneration of real tissue or organ is ideal. In dentistry, several regenerative treatments have been already applied clinically and new approaches for oral tissue regeneration including tooth regeneration are emerging.

In this current situation, I organized this symposium to discuss how regenerative treatment will implicate in dental implant treatment and to predict the treatment for edentulous patients in the next decade. In my opinion, tissue-engineering approaches for bone and soft tissue augmentation are real; however, whole tooth regeneration seems to be far from clinical application. Thus, in the next decade, it is likely that dental implant will be still effective for the treatment of edentulous patients and that new tissue-engineering techniques will simplify bone and soft tissue augmentation. It is expected that combination of dental implant treatment and new regenerative treatments will provide esthetical and functional outcome to a broad range of patients.

9:55 – 10:35

Akira YAMAGUCHI

Prof. of Oral Pathology, Graduate School, Tokyo Medical and Dental University, Japan

Molecular basis of bone regeneration and its application

Bone formation and regeneration are mediated by the coordinate action of various factors. Among these, bone morphogenetic protein (BMP) and runt-related gene 2 (Runx2) play crucial roles in bone formation. We demonstrated that BMP-2 not only stimulates osteoblastic differentiation of osteoprogenitors, but also transdifferentiates non-osteogenic mesenchymal cells to osteoblast lineage cells. Runx2 is essential for osteoblast differentiation and bone formation, since *Runx2*-deficient mice completely lack bone formation due to maturational arrest of osteoblasts. In addition, the overexpression of *Runx2* induces non-osteogenic cells to express osteoblast-related genes *in vitro*. These findings suggest that BMP and Runx2 are good candidates for cell-mediated gene therapy of bone repair. We conducted *in vitro* and *in vivo* experiments to search for explore a suitable technique for cell-mediated gene therapy of bone repair. These experiments were performed using skin fibroblasts isolated from green fluorescent protein (GFP) transgenic mice as a source for transplantation and adenovirus vectors encoding *BMP-2* and *Runx2* as tools for gene transfer. We demonstrated that skin fibroblasts isolated from GFP transgenic mice are an effective tool for tracing the fate of the transplanted cells during bone regeneration, and that transplantation of skin fibroblasts expressing *BMP-2* effectively promote bone repair. It will be important to investigate the interaction between BMP and other factors that up-regulates during bone regeneration.

10:35 – 11:25

Gregory R. MUNDY
Professor of Medicine, Pharmacology, Orthopaedics and Cancer Biology, Vanderbilt University Medical Center, USA

Statins as Mimics of BMP2 to Promote Bone Regeneration and Repair

BMP2 is a powerful biologic used extensively in a number of orthopedic applications where it has been shown to enhance bone restoration. However, its more widespread use has been limited by its expense, its method of delivery, and its stability. In order to overcome these problems, we have searched for compounds that mimic the biologic effects of BMP2. We have used the BMP2 promoter as a molecular target for screening small molecular weight compounds that mimic the effects of BMP2. We have identified a series of chemical compounds and natural products that increase BMP2 transcription by osteoblasts. We have found that enhancing endogenous BMP2 generation in bone stimulates bone formation systemically, and enhances rates of fracture healing in rats. Among the most powerful of the BMP2 mimics that stimulate bone formation in vivo are proteasome inhibitors and statins. Bortezomid is used clinically in myeloma and has been shown to increase BMP2 expression and alkaline phosphatase activity in patients administered this drug. Statins also increase bone formation systemically when given in large doses, or when administered transdermally or locally. This occurs because statins are subject to first pass metabolism, and bypassing the liver is necessary to achieve blood levels sufficient to produce beneficial effects on bone formation. The approach of using small molecules that mimic BMP2 effects without the disadvantages of peptide administration holds great promise as a practical therapeutic approach.

11:25 –11:45

Shohei KASUGAI

Prof. of Oral Implantology and Regenerative Dental Medicine, Graduate School, Tokyo Medical and Dental University

New Bone Substitute for Dental Implant Treatment: Combination with α-TCP and Simvastatin

Dental implant treatment is predictable; however if a patient does not have enough bone at the implant installation site, the treatment will be difficult. Although autologous bone graft is a gold standard for bone augmentation, inflammation of the donor site and limitation of harvestable bone volume are the problems. Bone substitutes are effective; however, they cannot take place of autologous bone. We have reported that α-TCP is smoothly exchanged for new bone when applied to the bone defects in animal experiments. On the other hand, simvastatin, a cholesterol-lowering drug, simulates BMP2 expression in osteoblasts enhancing bone formation when applied locally. Based on these evidences we have recently developed a bone substitute in combination with α-TCP and simvastatin, which acts as a scaffold for bone regeneration and simulates bone formation, finally being exchanged for bone. This bone substitute would be useful in dental implant treatment.

13:00 – 13:50

Rainer SCHMELZEISEN

Professor and Chair of Oral and Craniomaxillofacial Surgery , University Clinic Freiburg, Germany

Chair Side Stem Cell Application in Dentistry and Implantology

Clinically, autologous, allogenic and alloplastic materials for bone reconstructions in the craniomaxillofacial area have specific drawbacks necessitating the search for new (bio-) materials. Already today, cultivated skin and mucosa grafts are already in clinical routine use in head and neck reconstruction with good success.

In a clinical pilot study 45 sinusfloor augmentations in 32 patients were carried out at the department of Oral & Maxillofacial Surgery using a bone matrix derived from mandibular periosteum cells on a polymerefleece. In our hands there were 28 augmentations uneventful, in 17 procedures complications occurred. Other clinicians and private users had 64 procedures in 41 patients.

The results suggest that periosteum-derived osteoblasts on a suitable matrix form lamellar bone within 4 months after transplantation, thus providing a reliable basis for implant insertion. Nevertheless, in clinical investigation and radiological proof, grafting of tissue engineered bone gives overall results that are still not meeting the gold-standard of conventional bone grafts. They are an alternative especially in patients with simultaneous implant insertions.

Current research aims at investigating the influence of stem cells on biomaterials. In animal experiments stem cell application in combination with a bio material (Bio Oss) show lamellar bone formation and bone invasion into the micropores. Further evaluation of data is necessary to determine the possible future role of stem cells in augmentation procedures. Also methods of bioplotting of combined autologous/alloplastic materials are under investigation.In a clinical pilot study stem cells were used in 11 patients.

13:50 – 14:30

Hideaki KAGAMI

Associate Professor of Stem Cell Engineering, The Institute of Medical Science,
The University of Tokyo, Japan.

Tissue engineering of oral and maxillofacial tissues using somatic stem cells : Safety and efficacy of bone regeneration therapy using mesenchymal stem cells at the Institute of Medical Science Research Hospital: A preliminary report

Dental implants for partially or totally edentulous patients have recently become standard practice. However, edentulous alveolar ridges usually lack enough bone volume for implant placement. For patients with severe alveolar bone absorption, autogenous bone grafts or bioartificial bone substitutes have been used. Bioartificial bone substitutes are convenient but the ability for bone regeneration still seems limited. Although autogenous bone transplantation has been a gold standard, it requires a donor site and may cause morbidity. Accordingly, an alternative treatment to regenerate bone has been awaited. Bone regeneration using autogenous somatic stem cells has attracted much attention since this procedure does not require a donor site. Various cell types, including bone marrow-derived mesenchymal stem cells (MSCs), adipose-derived stem cells and periosteal cells, have proven useful for regenerating bone. MSCs can be harvested from bone marrow aspirate, which is a minimally invasive procedure. It is our aim to investigate the potential of bone regeneration using autologous MSCs and -tricalcium phosphate (-TCP) granules as a scaffold. Ten patients were recruited to the clinical study. Two of them were dropped because of possible contamination risk to the cultured cells or an insufficient number of cultured cells were acquired. The remaining patients underwent cell transplantation. The results from histological analyses of 5 patients showed bone regeneration and the average bone area was 43.8%. Interim results of this clinical study showed the potential of MSCs to enhance bone regeneration. However, a longer follow-up period is required.

14:30 – 15:10

Yuichi IZUMI

Professor of Periodontology, Graduate School, Tokyo Medical and Dental University

Periodontal Tissue Regeneration at Present and in the Near Future

Periodontitis is an inflammatory and infectious disease initiated by periodontopathic bacteria harboring on the root surfaces. It involves epithelial down growth with progressive destruction of the tooth supporting structures including the gingiva, periodontal ligament, root cementum and alveolar bone. The treatment of periodontitis consists of arrest of the periodontal disease progression by eliminating soft and hard deposits which have been formed and accumulated on the root surfaces, as well as creation of new periodontal environments which allow a proper and an easier cleaning of the root surfaces. In order to achieve this goal, the removal of inflammatory soft and hard periodontal tissues should be generally performed on the affected region. However, the ultimate goal of the periodontal treatment has been considered the regeneration of the periodontal tissue lost during the disease progression. Some regenerative techniques have been developed and introduced during the last two decades including bone grafting, root surface conditioning, guided tissue regeneration and application of growth factors. Although these treatments have been reported to be partly effective in regenerating periodontal tissues, their use in the daily clinical practice are still rather limited. Therefore, we are developing novel strategies applying tissue engineering for regeneration of periodontal tissues. The lecture will discuss the efficiency of application of mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP) complexes on periodontal bone defects, as well as a new technique using periodontal ligament cells sheet.

15:25 – 16:10

Takashi TSUJI

Professor, Faculty of Industrial Science and Technology, Tokyo University of Science, Tissue Engineering Research Center, Tokyo University of Science

Tooth Regeneration for a Future Organ Replacement Therapy

The ultimate goal of regenerative therapy is to develop fully functioning bioengineered organs that can replace lost or damaged organs after disease, injury or aging. The development of three-dimensionally reconstructed bioengineered organs from dissociated single cells *in vitro* is a goal of this technology. The “tooth” is a good feasibility study model in regenerative medicine because cells are easily obtained and even if extracted from an adult for study in the transplanted model, the process is rarely life-threatening. To bioengineer ectodermal organs such as teeth and whisker follicles, we developed a three-dimensional organ-germ culture method. The bioengineered tooth germ generated a structurally correct tooth, after both in vitro organ culture as well as transplantation under a tooth cavity *in vivo*, showing penetration of blood vessels and nerve fibers. Our model provides a substantial advance in the development of bioengineered organ replacement strategies and regenerative therapies. In this symposium, I would like to discuss why and explain how we are trying with the hardles of future tooth regenerative therapy, approached from organogenesis.