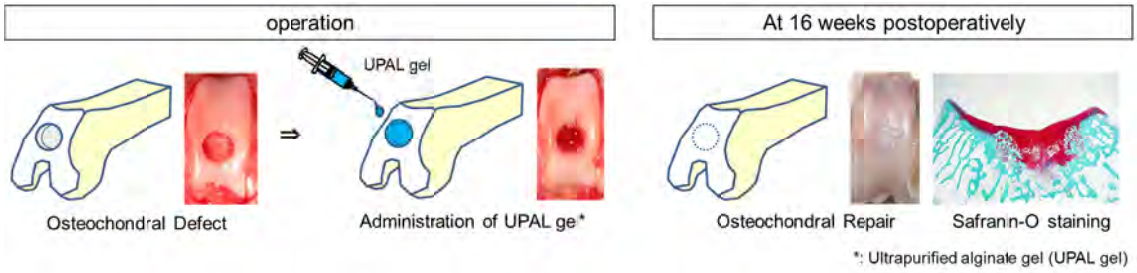
RESEARCH PROJECTS

CARTILAGE AND OSTEOARTHRITIS RESEARCH

(Norimasa Iwasaki, M.D., Onodera Tomohiro, M.D., Tadanao Funakoshi, M.D.**)**

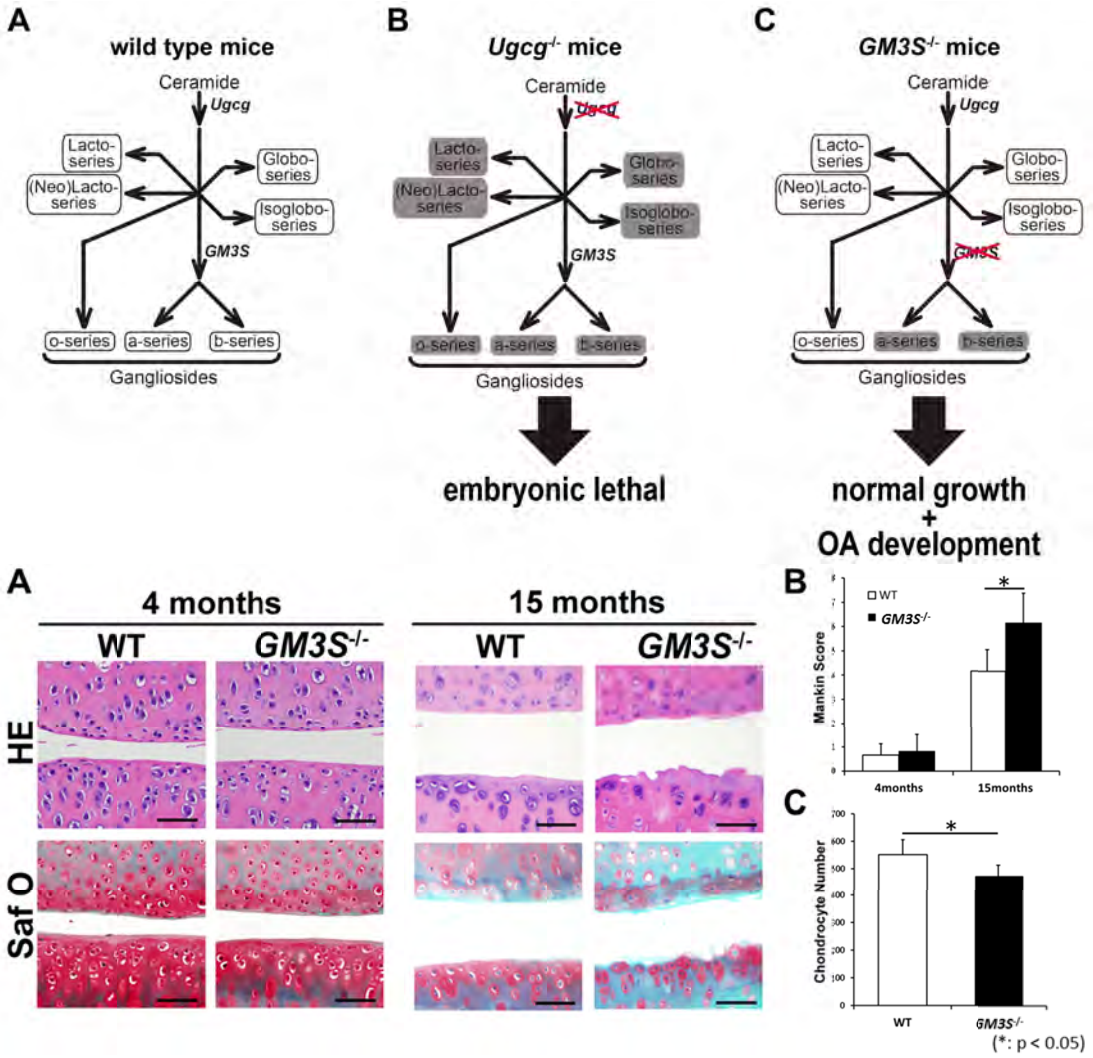
1）Tissue-engineering

Regarding tissue engineering in orthopaedic surgery, we think that the scaffold in which the cells appropriately differentiate and proliferate is the most important factor. Therefore, we have developed an original scaffold and employ it for the regeneration of cartilage, ligaments and tendons. The novelty of our scaffold is that it is a highly purified natural material which maximally reduces cytotoxicity. In addition, the components of the extracellular matrix, chemokines and cytokines can be administered into our scaffold to add bioactive functions, leading to excellent regenerative tissue. Reports on our unique projects encompassing collaboration between material biology and glycobiology have been published in many international journals and the projects are currently ongoing.



2）Osteoarthritis

Osteoarthritis（OA） is one of the most important diseases in orthopaedic surgery. Therefore, clarification of its pathogenesis and the development of new therapeutic strategies are urgently required. Regarding cartilage degradation, our laboratory, in collaboration with Prof. Shin-Ichiro Nishimura (Graduate School of Life Science, Hokkaido University) detected the glycostructures having important roles in the pathogenesis of OA. We are also collaborating with Prof. Tadashi Yamashita (Veterinary Biochemistry, Azabu University) and, by using several kinds of gene-modified mice, have clarified that glycosphingolipids are critical molecules to maintain cartilage homeostasis. A large animal model is being developed as a translational model for humans and our research projects should lead to clinical applications in the near future.

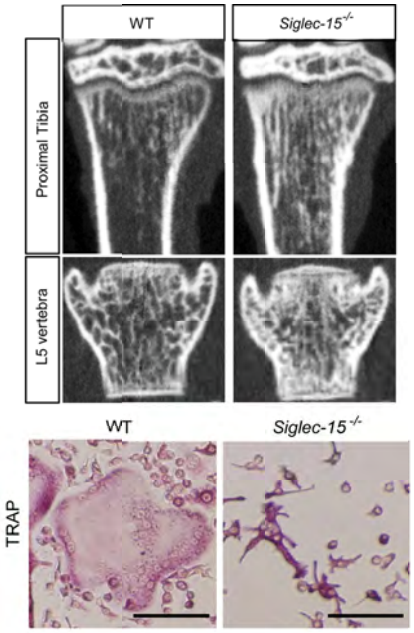


BONE RESEARCH

(Masahiko Takahata, M.D.**)**

1）Osteoclast biology

Osteoclasts are bone-resorbing cells with pivotal roles in destructive bone diseases and physiological bone remodeling. Therefore, understanding the mechanisms of osteoclast development is mandatory to develop better treatment options for bone diseases. We use a glycobiological approach to elucidate the mechanism of osteoclast development. We have found that cell surface sialylated glycans and sialic acid binding Ig-like lectin (Siglec)-15 play essential roles in developing functional osteoclasts, suggesting that glycans and their interacting molecules can be novel therapeutic targets for destructive bone diseases.

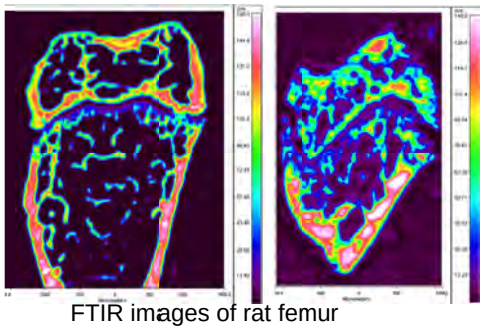


Mice lacking Siglec-15 show mild osteopetrotic phenolype due to impaired osteoclast development.

2) Bone quality study

In recent years, the concept of bone strength has moved beyond density alone and has expanded to include a number of characteristics of bone that collectively are called quality. Bone quality is determined by multiple factors including the microarchitecture, accumulated microscopic damage, quality of collagen, size of mineral crystals, and the rate of bone turnover. We recently established a novel technique for determination of the quality of fresh bone samples using infrared spectroscopy in collaboration with the Chitose Institute of Science and Technology.

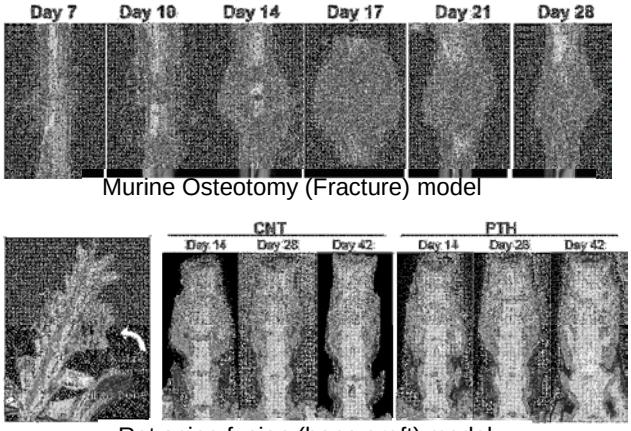
We use this new technique to analyze the bone quality in secondary osteoporosis such as glucocorticoid-induced osteoporosis. Our data will shed light on the pathomechanisms of bone fragility in patients with secondary osteoporosis.



FTIR images of rat femur

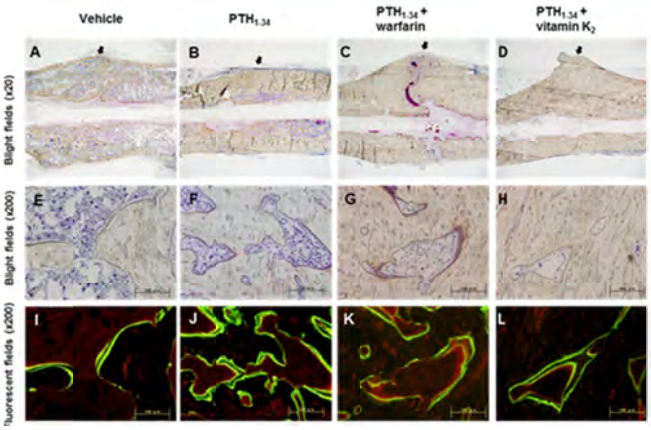
3) Fracture repair and bone graft healing

We are investigating the effects of bone metabolism-modifying agents such as teriparatide, bisphosphonates, SERM, and vitamin K on bone healing using a rodent osteotomy (fracture) model and bone graft model. These data will provide a substantial rationale for the choice of therapeutic drugs in osteoporotic patients with fracture and those undergoing bone graft surgery.



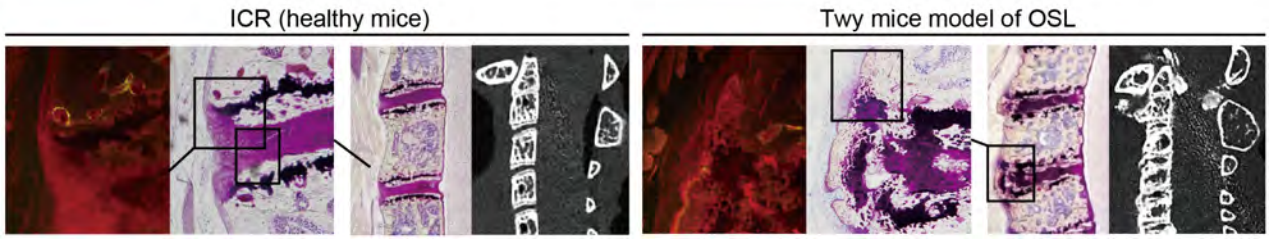
Murine Osteotomy (Fracture) model

Rat spine fusion (bone graft) model



4) Ossification of spinal ligaments

Ossification of spinal ligaments (OSL) is a pathologic condition that causes ectopic bone formation and subsequently results in various neurological deficits as well as spinal ankylosis; however, the etiology of OSL remains unknown. To control the development of ossification, we are investigating the effects of bone modifying agents, which possibly interfere with biomineralization or endochondral ossification, on the progression of ossification of spinal ligaments using a tiptoe-walking Yoshimura (twy) mouse model of OSL.

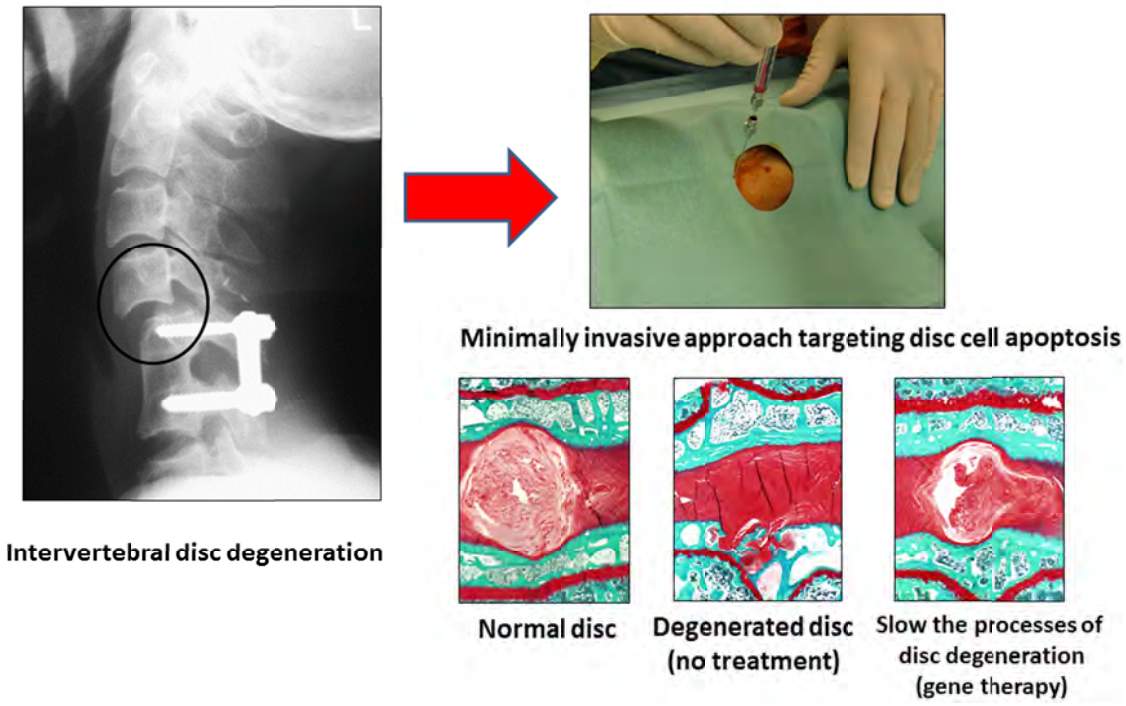


INTERVERTEBRAL DISC RESEARCH

(Hideki Sudo, M.D.)

Disc degeneration, disc cell apoptosis

Intervertebral disc (IVD) degeneration causes debilitating lower back pain in large segments of the worldwide population. No efficient treatment currently exists because of the unclear pathogenesis. One characteristic event early in the degeneration is the apoptosis of nucleus pulposus (NP) cells embedded in IVDs. Excessive biomechanical loading may also be a major etiology of IVD degeneration. We use in vitro and in vivo models of compressive loading to elucidate the underlying mechanisms of IVD degeneration. In addition, we are investigating whether the inhibition of apoptosis is a potential clinical therapeutic strategy for the treatment of IVD degeneration induced by biomechanical stress.



TENDON AND LIGAMENT RESEARCH

(Eiji Kondo, M.D.)

The research program in the Department of Advanced Therapeutic Research for Sports Medicine is collaborating with the Department of Orthopaedic Surgery and the Department of Sports Medicine and Joint Surgery of the Hokkaido University Graduate School of Medicine. Our major research areas are the following:

(1) In vivo and in vitro biomechanical studies on soft tissue graft materials for ligament reconstruction

(2) Biomechanical and biological studies for development of tissue engineering scaffolds and artificial organs in the treatment of ligament, tendon, meniscus and cartilage injuries

(3) Development of treatment strategies with clinically applicable biological materials

(4) Functional tissue engineering and clinical applications.

We have reported a number of our scientific studies in peer-reviewed journals. We have also conducted clinical studies on high tibial osteotomy performed with our original prosthesis. Recently, our technique for preservation of remnant ligament tissue in ligament reconstruction has attracted much notice in the clinical field.

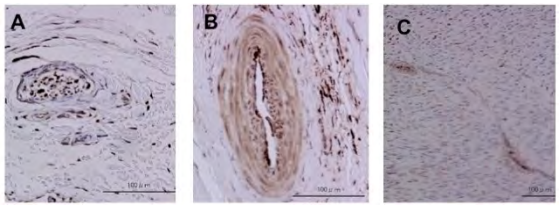


Fig 1. Mechanoreceptors and proprioceptive fibers were found in semitendinosus tendon autograft at 12 weeks after surgery.

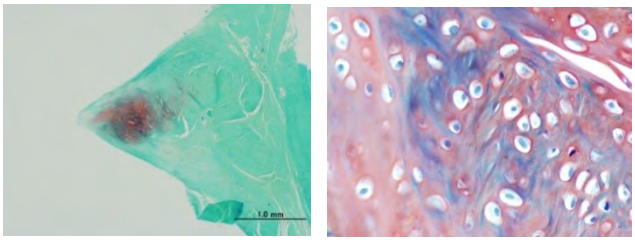


Fig 2. Implantation of autogenous meniscal fragments wrapped with a fascia sheath significantly induced fibrocartilage regeneration the meniscal defect.

OTHERS

1) Image processing (Tadanao Funakoshi, M.D.)

We focus on joint motion analysis using image processing. Our laboratory has developed original software for analysis of stress distribution across the joint surface together with the School of Engineering. A recent project is to apply for 4-dimensional motion image analyses. Pathological joint kinematics such as ligament insufficiency will be reproducible using these image processing methods.