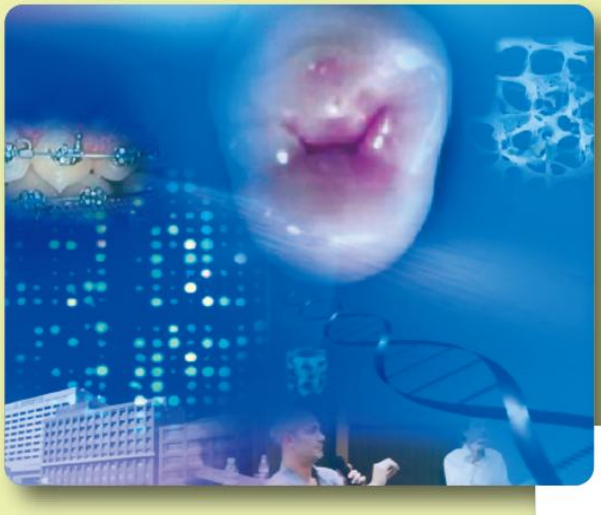
東京医科歯科大学　グローバルCOE

歯と骨の分子疾患科学の国際研究拠点

ーデント・メドミクスのインテリジェンスハブー

第2回 リトリート



【日程】

2010年

2月22日(月)9時～23日(火)5時頃

【場所】

ホテルグランド東雲

〒305-0034

茨城県つくば市小野崎涌井488-1

(TEL: 029-856-2212)

Tokyo Medical &Dental University
Global Center of Excellence Program

International Research Center for Molecular Science in Tooth and Bone Diseases

Second Retreat Camp

Feb.22-23,2010
At Hotel Grand Sinonome
488-1 Onozaki Tsukuba Ibaraki
Tel: 029-856-2212

東京医科歯科大学

日　程

1日目

時刻	プログラム
9.00-	東京医科歯科大から出発　バス
11.00-	到着予定　荷物を預ける
11.30-	自己紹介（学生とGCOEスタッフ） 予定より遅れた場合は省略
12.00-	昼食　（ポスターセットアップ）
13.00-	開会の挨拶　野田教授
13.10-14.10	Prof. Jane Aubin（トロント大）　50分 10分ディスカッション
14.10-15.00	辻　孝　先生（東京理科大）　40分 10分ディスカッション
15.00-15.30	Louisa Ho（トロント大院生）講演
15.30-15.40	休憩
15.40-16.00	前田由紀子先生（ハーバード大）
16.00-17.30	学生によるポスター 投票による優秀賞の選抜
17.30-17.45	Prof. Jane Aubin（Career Pathに関する講演）
17.45-18.35	シャペロンの研究キーワードについての談話
18.35-	夕食
19.30-20.45	シャペロンと学生の研究進路などについての 討論会

2日目

7.00-8.50	朝食
9.00-10.00	シャペロンによる口演発表 発表10分、ディスカッション2分
10.00-12.00	学生による口演発表 発表7分、ディスカッション3分
12.00-12.40	チェックアウト・昼食
JAXA	宇宙航空研究開発機構訪問 （大森 克徳先生、嶋津 徹先生、大島 博先生による講演）
13:30	集合・守衛室前
13:30-13:45	（バッチ配布）伏島、斉藤
13:45-14:45	各自展示室、お土産（60分）個人行動
14:45	ロケット前に再集合　伏島、斉藤
14:45-15:00	（移動・実験棟）
15:00-15:20	嶋津さん講演（20分）
15:20-15:40	大森さん講演（20分）
15:40-16:00	大島さん講演（20分）
16:00-16:15	（移動・守衛室）
16:15	バッチ回収・解散
17.00-	医科歯科大へ到着

Schedule

1st day

time	programme
9.00-	departure from TMDU by bus activities on bus
11.00-	approximate arrival arrange baggage (luggage reception?)
11.30-	self introduction (all students and COE staffs) if schedule becomes late, skip this part briefly
12.00-	lunch (poster setup)
13.00-	opening speech by Prof. Noda
13.10-14.10	Prof. Jane Aubin (University of Toronto) 50 min presentation　10min discussion
14.10-15.00	Prof. Takashi Tsuji (Tokyo University of Science) 40 min presentation　10min discussion
15.00-15.30	Louisa Ho (graduate student, University of Toronto)
15.30-15.40	break
15.40-16.00	Dr. Yukiko Maeda (Harvard Univ.)
16.00-17.30	student poster presentation Selection of Excellent posters
17.30-17.45	Prof. Jane Aubin (University of Toronto) Career Path
17.45-18.35	chaperone key word discussion
18.35-	dinner
19.30-20.45	chaperone/prof. activity/ discuss in general topics

2nd day

7.00-8.50	breakfast
9.00-10.00	chaperone oral presentation 10 min. present/ 2 min discussion
10.00-12.00	student oral presentation 7 min. present/ 3 min discussion
12.00-12.40	check out /lunch
13.00-15.30	visiting lab　JAXA (Tsukuba, Lectures by Drs. Oshima, Oomori, and Shimazu)
17.00-	back to TMDU

事業推進担当者

Masaki Noda, M.D., Ph.D.
(野田政樹)
GCOE Program Leader, Professor
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http://www.tmd.ac.jp/mri/mph/index.html

Junji Tagami D.D.S., Ph.D.
(田上順次)
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Department of Cariology and Operative Dentistry
http://www.tmd.ac.jp/grad/ope/ope-J.htm

Hiroshi Takayanagi, M.D., Ph.D.
(高柳広)
Department of Cell Signaling
http://www.tmd.ac.jp/grad/csi/csi-J.htm

Ikuo Morita, Ph.D.
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http://www.tmd.ac.jp/dent/cell/cell-J.htm

Ken Omura, D.D.S., Ph.D.
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Department of Oral and Maxillofacial Surgery
http://www.tmd.ac.jp/dent/os2/os2-J.htm

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http://www.tmd.ac.jp/grad/mfc/mfc-J.htm

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http://www.tmd.ac.jp/dent/endo/endo-J.htm

Yuichi Izumi, D.D.S., Ph.D.
(和泉雄一)
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http://www.tmd.ac.jp/dent/peri/peri-J.htm

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http://www.tmd.ac.jp/grad/bch/bch-J.htm

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http://www.tmd.ac.jp/dent/opat/opat-J.htm

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http://www.tmd.ac.jp/grad/mort/mort-J.htm

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http://www.tmd.ac.jp/med/orth/orth-J.html

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http://www.tmd.ac.jp/grad/rheu/rheu-J.htm

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http://www.tmd.ac.jp/med/orth/orth-J.html

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Department of Organic Materials
http://www.tmd.ac.jp/i-mde/www/org/jpn/index.html

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http://www.tmd.ac.jp/mri/cgen/framepage.htm

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http://www.tmd.ac.jp/mri/mgen/index_j.html

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Department of Molecular Cell Biology
http://www.tmd.ac.jp/mri/mri-mcb/index_j.html

Yoshihiro Ogawa, M.D., Ph.D.
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http://www.tmd.ac.jp/mri/prm/index.html

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(萩原正敏)
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Department of Molecular Medicine and Metabolism
http://www.tmd.ac.jp/mri/mri-end/index.html

Nobuhiro Hanada,
(花田信弘)
Professor

国際PIシャペロン、AISS・QAISS

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(納富拓也)
Research Assistant Professor
Department of Molecular Pharmacology

Alireza Sadr, D.D.S., Ph.D.
Research Assistant Professor
Department of Cariology and Operative Dentistry

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(大洞将嗣)
Research Associate Professor
Department ofCell Signaling

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(中村博幸)
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Department of Hard Tissue Engineering
Biochemistry

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Department of Orthopedic Surgery

Lee Jiyoung, Ph.D.
(李知英)
Research Assistant Professor
Department of Epigenetics

Naoki Sawada, M.D., Ph.D.
(澤田直樹)
Research Assistant Professor
Department of Molecular Medicine and Metabolism

Paksinee Kamolratanakul
Dept. of Molecular Pharmacology
「ナノゲルscaffoldを用いたEP4アゴニストとBMPの
骨再生能に関する研究」

中川　朋美
Tomomi Nakagawa
Dept. of Molecular Pharmacology
「悪性黒色腫の骨の転移における転写因子Cizの
役割の解明」

Patricia Makishi
Dept. of Cariology and Operative Dentistry
「レジンセメントと象牙質界面における
ナノリーケージについて」

林　幹人
Mikihito Hayashi
Dept. of Cell Signaling
「破骨細胞の分化ステージ特異的な
NFATc1標的遺伝子の同定」

青井　陽子
Yoko Aoi
Dept. of Cellular Physiological Chemistry
「低酸素下におけるサイトカイン産生変動機序～
メチル化の関与」

Chalida Nakalekha
Dept. of Cellular Physiological Chemistry
「骨代謝におけるプロスタサイクリンの役割」

Rajib Bhattacharjee
Dept. of Cellular Physiological Chemistry
coment
「骨芽細胞におけるコネキシン43発現の調節機構の解明」

津川　順一
Junichi Tsugawa
Dept. of Cellular Physiological Chemistry
「印刷技術を用いて羊膜に転写した細胞による
骨再生療法の確立」

長岡　亮介
Ryosuke Nagaoka
Dept. of Cellular Physiological Chemistry
「顔面形態形成に対する低酸素の影響」

Hudieb Malik Ismail
Dept. of Oral Impltantology & Regenerative Dental Medicine
「インプラントと骨再生との生物物理学的関係」

MYAT NYAN
Dept. of Oral Impltantology & Regenerative Dental Medicine
「Simvastatin 含有α - TCPを用いた骨再生に関する研究」

Reena Rodriguez
Dept. of Oral Impltantology & Regenerative Dental Medicine
「Epigallocatechin-3-gallate 含有 Gelatin Hydrogelを
用いた骨再生に関する研究」

伊達　佑生
Yuki Date
Dept. of Oral Impltantology & Regenerative Dental Medicine
「歯根発生に関する因子の同定」

則武　加奈子
Kanako Noritake
Dept. of Oral Impltantology & Regenerative Dental Medicine
「スーパーGBR膜「ハイドロゲルシート」の開発」

Gombo Balortuya
Dept. of Pulp Biology and Endodontics
「インテグリン発現を評価することによる象牙芽細胞の
成熟とシグナル伝達に対する低出力レーザー療法の効果」

Aleksic Verica
Dept. of Periodontology
「歯周疾患は動脈疾患の進行に重要な
リスクファクターとなる」

Aslam Al Mehdi
Dept. of Periodontology
「歯周疾患は動脈疾患の進行に重要な
リスクファクターとなる」

Gamaralalage Amodini Rajakaruna
Dept. of Periodontology
「歯周病とバージャー病の関連の解明」

新垣　理宣
Tadanobu Aragaki
口腔病理学分野
角化嚢胞性歯原性腫瘍の生物学的特徴
Biological characteristics of Keratocystic odontogeneic tumors

Ganburged Ganjargal
Dept. of Maxillofacial Orthognathics
「マルファン症候群における重篤な歯周炎の
分子機構について」

鈴木　尋之
Hiroyuki suzuki
Dept. of Maxillofacial Orthognathics
「可溶型 fibroblast growth factor receptor2 (FGFR2) の
頭蓋冠縫合部早期癒合症に対する治療効果」

木村　文子
Ayako Kimura
Dept. of Orthopaedic and Spinal Surgery
「軟骨細胞の分化調節機構の解明
-軟骨組織特異的Runx1マウスを用いた検討-」

菅田　祐美
Yumi Sugata
Dept. of Orthopaedic and Spinal Surgery
「HApColとビスフォスフォネート局所徐放による
骨悪性腫瘍の治療法の開発」

白　樺
Bai Hua
Dept. of Moleclurar Cytogenetics
「ヒト癌におけるオートファジー関連遺伝子
LC3Av1 遺伝子の機能解析」

呂　正光
Lu ZhengGang
Dept. of Molecular Genetics
「転移性骨腫瘍をターゲットとしたNF-kappa B活性
制御機構解明」

岩舩　浩孝
Hirotaka Iwafune
Epigenetics
ゲノムインプリンティング　リプログラミング変異体の単離とその解析
Analysis of reprogramming mechanism of genomic imprinting in mice

Samir Kumar Pal
口腔病理学 (Oral Pathology)
口腔扁平上皮癌による骨破壊における
Thrombospondin-1の役割
The Role of Thrombospondin-1 (TSP-1) in Bone Destruction by Oral Squamous Cell Carcinoma

下田　麻子
Asako Shimoda
有機材料 (Organic materials)
ナノゲル架橋ハイドロゲルによるタンパク質デリバリー
Design of Nanogel-assembled hydrogel for protein delivery

高橋　治子
Haruko Takahashi
有機材料（Organic materials）
Polysaccharide nano-ball を用いた新規ナノキャリアの開発
Design of Funtional Polysaccharide nano-ball as new nanocarrier

木原　翼
Tasuku Kihara
Oral pathology
骨芽細胞分化と骨再生におけるCCN3の役割
The role of CCN3 in osteoblast differentiation and bone regeneration

古田　繭子
Mayuko Furuta
分子細胞遺伝学（Molecular Cytogenetics）
新たなRNA創薬に寄与する癌制御性microRNAの機能的スクリーニング
Exploration of novel tumor-suppresive microRNAs using functional genomics-assisted approach

姫野　彰子
Akiko Himeno
バイオイメージングを用いた歯周組織幹細胞の同定
Identification of periodontal stem cells by bio-imaging approaches

辻　香織
Kaori Tsuji
顎顔面矯正学
Zinc finger 型転写因子POKEMONの破骨細胞における役割の解明
Investigation of the role of zinc finger transcription factor, POKEMON in osteoclasts

Amir Nazari
う蝕制御学
う蝕脱灰象牙質を高度石灰化組織へと変化させるための再石灰化技術の創造
Developing a Dentin Remineralising Method（DRM）to Transform Carious Demineralised Dentin into Hypermineralised Substrate

許　レン
XU Ren
整形外科（Orthopaedic and Spinal Surgery）
視床下部性神経ペプチドによる中枢性骨代謝制御機構の解明
Uncovering the molecular mechanism of central control of bone remodeling by hypothalamic neuropeptides

周　夢宇
Zhou Mengyu
歯髄生物学（Pulp Biology and Endodontics）
歯根形成のメカニズム -SCAP（根尖部幹細胞）からの象牙芽細胞およびセメント芽細胞分化に関与する因子の解明
The mechanisms of root formation- Elucidation of the signaling molecules on odontoblast and cementoblast differentiation from SCAP

Smriti Aryal
分子薬理学（Molecular Pharmacology）
細胞骨格による骨代謝制御の分子機構 -Nckの骨の細胞機能調節に於ける役割の解明-
Molecular Mechanisms Underlying Cytoskeletal Regulation of Bone Metabolim-Role of Nck Proteins in Bone Cell Function-

松本　力
Tsutomu Matsumoto
口腔病理学
矯正的歯の移動における骨細胞の役割
The role of osteocyte in orthodontic tooth movement

Chokechanachaisakul Uraiwan
歯髄生物学（Pulp Biology and Endodontics）
ラットを用いた歯髄生物学
Rat's pulp biology

Kunawarote Sitthikorn
う蝕制御学
う蝕象牙質に対する接着性能の改良
Improve Bond strength to Caries-affected dentin

Ilnaz Hariri
う蝕制御学
高度に石灰化した接着界面構造の作成と機械的性質の評価
Generation of hyper mineralized adhesive Interface and study on its mechanical properties

AL-Bari MD. ABDUL
分子情報伝達学（Cell Signaling）
破骨細胞分化を制御するphosphatidylinositol-3,4,5-trisphosphate結合タンパク質の同定と機能解析
Identification and analysis of phosphatidylinositol-3,4,5-trisphosphatebinding proteins（PIP_3BPs）that regulate osteoclast differentiation

古市　祥子
Akiko Furuichi
インプラント・口腔再生医学
酸素ナノバブル水の骨組織における生体活性評価
Evaluation for the biologically activity of oxygen nano bubbles solution（OXNB）

Hamid Nurrohman
う蝕制御学（Cariology and Operative Dentistry）
人口口腔装置を用いたバイオフィルムによるう蝕形成後の"Super Dentin"のナノ構造解析
The effect of collagenolytic inhibitors on the quality of acid-base resistant zone in dentin

Chui Chanthoeun
歯周病学（Periodontology）
歯周組織の除菌のための新しい治療様式の開発:LEDと光感受性色素を用いた抗菌的光線力学療法の効果に関する基礎的研究
Development of a New Treatment Modality for Periodontal Disinfection: Basic Study on the Effect of Antimicrobial Photodynamic Therapy using the Combination of an LED light Source and a Photosensitizing Dye

Wayakanon Praween
分子細胞機能学（Cellular Physiological Chemistry）
アニュラーギャップジャンクションの形成機構
The Mechanisms of Annular Gap Junction Formation

村松　智輝
Tomoki Muramatsu
分子細胞遺伝学（Molecular Cytogenetics）
食道扁平上皮癌の発生・進展におけるYAP増幅・発現亢進の分子病理学的意義
Significance of YAP amplification/overexpression in the pathogenesis of esophageal squamous cell carcinoma

鈴木　允文
Suzuki Takafumi
歯周病学
骨吸収を引き起こす咬合性外傷の分子機構について解析する-TRPV4の役割-
Molecular mechanism underlying occlusal trauma, induced-bone loss Role of TRPV4

Bhargava Suhas Srilatha
インプラント・口腔再生医学
表面改良型Y-TZPジルコニア:骨再生に関する生体外及び生体内の研究
Surface modified Y-TZP Zirconia: an in vitro and in vino study of bone formation

Atukorallaya Devi Sewvandini
硬組織構造生物学（インプラント・口腔再生医学）
小型硬骨魚メダカの顎歯と咽頭歯の発生誘導に及ぼすエクトディスプラシン情報伝達経路の役割の解析と歯の進化の検討
Evolutionarily conserved role of ectodysplasin signaling in odontogenesis of ectodermally and endodermally induced teeth in small-sized teleost fish medaka

宮嶋　大輔
Daisuke Miyajima
顎顔面外科（分子薬理）
骨代謝における負のMCSFシグナルによる新制御機構の解析
-Dok　アダプター分子による破骨細胞制御と骨粗鬆症-
Novel Insights into Negative Molecular Regulation of MCSF Signaling in Bone Metabolism -Function of Dok Adaptor Molecules in Osteoclasts and Osteoporois -

Rojbani Hisham Khalifa
implantology
異なる骨補填剤（アルファ　TCP,ベータTCP, HA）とシンバスタチン投与の有無におけるラットでの骨形成に関する比較研究
A comparative study of the effect of three different Bone substitute materials (a-TCP,B-TCP,and HA) on the formation of new bone with and without the use of Simvastatin

チェン　康
Chen Kang
インプラント・口腔再生医学（Dental Implantology & Oral Regenerative Medicine）
歯科用インプラント周囲骨における直流電流装置を用いた骨形成促進作用に関する研究
A direct current device for accelerating bone formation in tissues surrounding a dental implant

Osama Zakaria
インプラント・口腔再生医学
GBRと骨膜ディストラクション法による軟組織の同時骨再生のための新規開発装置の評価
Evaluation of a new device for bone regeneration by GBR and periosteal distraction simultaneously with soft tissue distruction

Khandakar Abu Shameem Md. Saadat
分子発生学（分子細胞機能学）
RB/E2F　経路の制御と骨肉腫形成過程におけるDRIL1の役割
The Role of DRIL1 in the Regulation of RB/E2F Pathway and Tumorigenesis of Osteosarcoma

Erik Idrus
Dept. of Cell Signaling
「RANKL刺激によるNFATc1制御遺伝子とmicroRNAの同定」

藤田　浩二
Koji Fujita
Dept. of Orthopaedic and Spinal Surgery
「Vitamin Eの骨代謝に対する影響について」

王　慧峰
Wang HuiFeng
Dept. of Molecular Genetics
「新規BRCA2関連遺伝子Nucleophosmin（NPM）の同定と機能解析」

$Gja^{Jrt/+}$ mice are protected from age-related bone loss

Jane E. Aubin

Department of Molecular Genetics, University of Toronto, Toronto, ON

Oculodentodigital dysplasia (ODDD) is an autosomal dominant disorder characterized by pleiotropic developmental anomalies of the limbs, teeth, face and eyes that was shown recently to be caused by mutations in the gap junction protein alpha 1 gene (GJA1), encoding connexin 43 (Cx43). In the course of performing an Nethyl-N-nitrosourea mutagenesis screen, we identified a dominant mouse mutation that exhibits many classic symptoms of ODDD, including syndactyly, enamel hypoplasia, craniofacial anomalies and cardiac dysfunction. Positional cloning revealed that these mice carry a point mutation in Gja1 leading to the substitution of a highly conserved amino acid (G60S) in Cx43. In vivo and in vitro studies revealed that the mutant Cx43 protein acts in a dominant-negative fashion to disrupt gap junction assembly and function. Notably, in addition to the classic features of ODDD, $Gja^{Jrt/+}$ mice exhibit osteopenia throughout life, with delayed ossification of all bones, but the difference in bone mineral density (BMD) compared to wild type littermates becomes less pronounced with age, i.e., $Gja^{Jrt/+}$ mice are protected form the age-related bone loss seen in wild type mice. Cellular assays showed that osteoclast number is normal or even slightly reduced but activity is higher in younger but not older $Gja^{Jrt/+}$ versus wild type mice. On the other hand, osteoblast number in vivo and osteoprogenitor number in stromal cell cultures in vitro display a trend towards being increased in older animals, i.e., in mice at 8 and 12 months of age. In addition, while no differences were seen in osteoblast-associated marker expression at early differentiation times, expression of several mature osteoblast and osteocyte markers was significantly higher at late differentiation time points in bones and stromal cultures of $Gja1^{Jrt/+}$ versus wild type mice. Our results indicate that while complete ablation of Cx43 and the presence of a dominant-negative allele of Cx43 both lead to low bone mass phenotypes, the underlying cellular mechanisms are notably different. In particular, our data show that diminution of Cx43 expression and function via the G60S mutation affects bone modeling and remodeling by dysregulation of both osteoclast and osteoblast lineage cells, that the osteopenia seen may reflect primarily increased osteoclast activity in younger mice, but that this is balanced by an increased osteoblast activity, the latter protecting GjaJrt/+ mice from the age-related bone loss seen in wild type mice.

Academic Background

09/1968–06/1972	Bachelor of Science (Honours), Chemistry/Mathematics, Queen's University at Kingston, CANADA
07/1972–02/1977	Doctorate (PhD),, Medical Biophysics, University of Toronto, CANADA (Dr. Victor Ling)
07/1977–06/1978	Postdoctorate, Max Planck Institute for Biophysical Chemistry, GERMANY (Dr. Tom Jovin)
07/1978–06/1979	Postdoctorate, Max Planck Institute for Biophysical Chemistry, GERMANY (Dr. Klaus Weber)

Work Experience

07/1979–06/1983	Assistant Professor, Dentistry-Oral Biology / MRC Group in Periodontal Physiology, University of Toronto, CANADA
07/1983–06/1988	Associate Professor, Dentistry-Oral Biology / MRC Group in Periodontal Physiology, Faculty of Dentistry, University of Toronto, CANADA
07/1988–06/1994	Full Professor, Dentistry-Oral Biology / MRC Group in Periodontal Physiology ,Faculty of Dentistry, University of Toronto, CANADA
07/1988–06/1994	Director and Chair, Graduate Department of Dentistry / Director Postgraduate Dental Education, Faculty of Dentistry, University of Toronto, CANADA
07/1994–06/2002	Professor and Chair, Anatomy and Cell Biology, Faculty of Medicine, University of Toronto, CANADA
02/2003–12/2005	Scientific Co-Director and CEO, NCE, Networks of Centres of Excellence, Canadian Arthritis Network, CANADA
01/2006–12/2006	Scientific Director and CEO, NCE Network of Centres of Excellence, Canadian Arthritis Network, CANADA
07/1999–	Full Professor, Medical Biophysics, Faculty of Medicine, University of Toronto, CANADA
07/2002–	Full Professor Medical Genetics and Microbiology, Faculty of Medicine, University of Toronto, CANADA
01/2007–	Scientific Director, Institute of Musculoskeletal Health and Arthritis, Canadian Institutes of Health Research, CANADA

Distinctions

06/1970	Canadian Rosebourgh Award - Book Prize, Canadian Chemical Society, CANADA
06/1971	Analytical Chemistry Award, Queen's University, CANADA
06/1972	Gold Medal Graduation Award, Queen's University, CANADA
03/1985	Oral Biology Research Award, International Association for Dental Research
10/2004	The William F. Neuman Award, American Society for Bone and Mineral Research, UNITED STATES
09/2005	Louis V. Avioli Memorial Lecture, American Society for Bone and Mineral Research, UNITED STATES

Councils and Leadership Roles (selected):

1997-2000	Board of Directors, Advances in Mineral Metabolism
1998-1999	President, American Society for Bone and Mineral Research (ASBMR)
2000-2002	Chair, Science Policy Committee, ASBMR
1998-2001	Member of Executive, AACBNB Chairpersons (US)
2001-2006	Advisory Board, Institute of Musculoskeletal Health and Arthritis, CIHR; Vice-Chair, 2005-2006
2001-present	Member, Board of Directors, Canadian Arthritis Network NCE
2002-2006	Member, Board of Directors, and Public Affairs Executive Committee, FASEB
2003-2007	Member of the Board, International Bone and Mineral Society
2004-present	Member, Finance Committee, American Society for Cell Biology
2004	Co-Chair, Long range planning advisory committee in research in Bone Biology and Bone Diseases, NIAMS/NIH
2005-2007	President-Elect, International Bone and Mineral Society

Publications (selected)

1. Bonnelye E, Laurin N, Jurdic P, Hart DA, Aubin JE. Estrogen receptor-related receptor-{alpha} (ERR-{alpha}) is dysregulated in inflammatory arthritis. Rheumatology 2008
2. Hasegawa T, Oizumi K, Yoshiko Y, Tanne K, Maeda N, Aubin JE. The PPARgamma-selective ligand BRL-49653 differentially regulates the fate choices of rat calvaria versus rat bone marrow stromal cell populations. BMC Dev Biol. 2008 ;8:71.

3. Malaval L, Wade-Guéye NM, Boudiffa M, Fei J, Zirngibl R, Chen F, Laroche N, Roux JP, Burt-Pichat B, Duboeuf F, Boivin G, Jurdic P, Lafage-Proust MH, Amédée J, Vico L, Rossant J, Aubin JE. Bone sialoprotein plays a functional role in bone formation and osteoclastogenesis. J Exp Med. 2008; 205(5):1145-53.
4. Zirngibl RA, Chan JS, Aubin JE. Estrogen receptor-related receptor alpha (ERRalpha) regulates osteopontin expression through a non-canonical ERRalpha response element in a cell context-dependent manner. J Mol Endocrinol. 2008; 40(2):61-73.
5. Falconi D, Aubin JE. LIF inhibits osteoblast differentiation at least in part by regulation of HAS2 and its product hyaluronan. J Bone Miner Res. 2007; 22(8):1289-300.
6. Yoshiko Y, Candeliere GA, Maeda N, Aubin JE. Osteoblast autonomous Pi regulation via Pit1 plays a role in bone mineralization. Mol Cell Biol. 2007; 27(12):4465-74.
7. Bonnelye E, Zirngibl RA, Jurdic P, Aubin JE. The orphan nuclear estrogen receptor-related receptor-alpha regulates cartilage formation in vitro: implication of Sox9. Endocrinology. 2007; 148(3):1195-205.
8. Zhang S, Chan M, Aubin JE. Pleiotropic effects of the steroid hormone 1,25-dihydroxyvitamin D3 on the recruitment of mesenchymal lineage progenitors in fetal rat calvaria cell populations. J Mol Endocrinol. 2006; 36(3):425-33.
9. Liu F, Malaval L, Aubin JE. Global amplification polymerase chain reaction reveals novel transitional stages during osteoprogenitor differentiation. J Cell Sci. 2003; 116 (Pt 9):1787-96.

Tooth Regenerative Therapy as a Future Organ Replacement Regenerative Therapy

Takashi Tsuji, PhD

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Organ Technologies Inc.

To restore the partial loss of organ function, stem cell transplantation therapy has been developed as a cure for various diseases conditions, such as Parkinson's disease, leukemia, spinal injury, cardiac infarction, diabetes and liver diseases. 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. However, no technology yet exists that enables us to create and grow organs through the single cell manipulation.

Almost all organs including tooth arise from the organ germs, which are induced by the reciprocal epithelial-mesenchymal interactions in the developing embryo. It has been proposed a novel concept for a bioengineered organ development that to properly reproduce the developmental process of organogenesis. To demonstrate the possibility of this concept, we attempted to develop a tooth regenerative therapy for lost tooth, which were challenged from the transplantation of a bioengineered tooth germ in adult oral environment as a model of a future organ replacement therapy. In the dental field, the therapy, such as "bridge" and "implant", had been established to prevent the movement of the neighboring teeth and supplement of their functions for the loss of the tooth by injury, caries or diseases. Therefore, "tooth" provides a good feasibility study model for the development of the technologies for a future organ replacement regenerative therapy.

In current research on whole-tooth regenerative therapy, a basic strategy is being pursued in which a bioengineered tooth germ is induced to develop into a fully functional tooth. Previously, we developed a three-dimensional organ-germ culture method for the reconstitution a bioengineered organ germ in the early developmental stages (Nature Methods 2007). The regeneration of tooth and periodontal tissues into a functional tooth unit is a critical issue for achieving proper oral function, including mastication. Recently, we successfully demonstrated that our bioengineered tooth germ could develop a fully functioning tooth, which has hardness for masticatory potential, the functional responsibility against a mechanical stress in maxillofacial region, and perceptive potentials of neural fibers innerved into the periodontal ligament and pulp of the bioengineered tooth to noxious stimulations such as orthodontic treatment and a pulp stimulation (PNAS 2009). These results showed that the bioengineered tooth germ could develop a fully functioning regenerated tooth in vivo after engraftment and an organ replacement regenerative therapy using a bioengineered organ germ might be feasible.

In this presentation, I will talk and discuss about the strategies and recent progress of the research for the establishment of tooth regenerative therapy.

Figure:
Micro-CT analysis of a bioengineered tooth erupted in adult oral environment at 50days after transplantation. Arrow-head indicates the bioengineered tooth

References:

1. Ikeda, E. et al., Fully functional bioengineered tooth replacement as an organ replacement therapy, Proc. Natl. Acad. Sci. USA., 106 (32), 13475-13480, 2009.
2. Ikeda, E. & Tsuji, T., Growing bioengineered teeth from single cells: potential for dental regenerative medicine., Expert Opinion on Biological Therapy 8, 1-10, 2008.
3. Nakao, K., Morita, R., Saji, Y., Ishida, K., Tomita, Y., Ogawa, M., Saitoh, M., Tomooka, Y. & Tsuji, T..: The development of a bioengineered organ germ method, Nature Methods 4, 227-230, 2007.

Education

1993	PhD Graduate School of Science and Technology, Niigata University, Japan
1989-1992	Graduate School of Science, Kyushu University, Japan
1986	MSc Graduate School of Science, Niigata University, Japan
1984	BSc Faculty of Science, Niigata University, Japan

Professional Career

2009-Present	Professor, Research Institute for Science and Technology, Tokyo University of Science
2007-2009	Professor, Faculty of Industrial Science and Technology, Tokyo University of Science
2000-2007	Associate Professor, Faculty of Industrial Science and Technology, Tokyo University of Science
1993-2000	Senior Researcher, Pharmaceutical Frontier Research Laboratory, Japan Tobacco Inc.
1986-1989	Researchers, Central Research Laboratories, Yamanouchi Pharmaceutical Co Ltd.

Other Career

2008-Present	Director, Organ Technologies Inc.
2008	Visiting Professor, Louis Pasteur University
2004-Present	Advisor, Otsuka Chemical Co., Ltd.

Academic Activities

2007-Present	Director, the Japanese Association for Regenerative Dentistry
2006-Present	Councilor, the Japan Society for Organ Preservation and Medical Biology
2002-Present	Councilor, the Japanese Society for Regenerative Medicine

Etsuko Ikeda, Ritsuko Morita, Kazuhisa Nakao, Kentaro Ishida, Takashi Nakamura,Teruko Takano-Yamamoto, Miho Ogawa, Mitsumasa Mizuno, Shohei Kasugai, and Takashi Tsuji. Fully functional bioengineered tooth replacement as an organ replacement therapy. PNAS 106, 13475–13480, 2009

Ryu-ich Fukuda, Kiyohito Tsuchiya, Koji Suzuki, Katsuhiko Itoh, Jun Fujita, Atae Utsunomiya,and Takashi Tsuji, HTLV-I Tax downregulates the expression of PIP3 inositol phosphatases via the NF-kB pathway. J. Biol. Chem. 284, 2680-2689, 2009.

Takashi Tsuji. Pluripotent stem cells developed into regenerated tooth by organ germ method in combination with tooth germ-derived epithelium. Proceeding of International Symposium on Micro-Nanomechatronics and Human Science 2007, 342-346, 2007.

Kazuhisa Nakao, Ritsuko Morita, Yasumitsu Saji, Kentaro Ishida, Miho Ogawa, Masahiro Saitoh, Yasuhiro Tomooka & Takashi Tsuji. The development and in vivo transplantation of an artificial tooth germ reconstituted by the bioengineered organ germ method. Eur Cell Mater. 14, 59, 2007

Kazuhisa Nakao, Ritsuko Morita, Yasumitsu Saji, Kentaro Ishida, Yusuke Tomita, Miho Ogawa, Masahiro Saitoh, Yasuhiro Tomooka & Takashi Tsuji. The development of a bioengineered organ germ method. Nature Methods. 4, 227-130, 2007.

Gli2 and p53 interactions in Hedgehog-induced Tumorigenesis

Louisa Ho[1,3]

Aneta Stojanovski[1,3], Heather Whetstone[1], Qing Xia Wei[1], Elaine Mau[1], Jay Wunder[2], Benjamin Alman[1,2]

[1] Program in Developmental and Stem Cell Biology, Hospital for Sick Children, University of Toronto, Toronto ON, M5G 1L7.
[2] Department of Surgery, Mount Sinai Hospital, University of Toronto, Toronto, ON.
[3] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON

Enchondromas are common benign cartilage tumors that arise in bones that undergo endochondral ossification, and may progress to malignant chondrosarcoma. Development of enchondroma results from abnormal regulation of Indian hedgehog (Ihh) signaling during growth plate development. As well, mutations in p53 have been detected in chondrosarcoma, and are thus suspected to play a role in its progression. Our lab has previously shown that enchondroma develop in transgenic mice in which overexpression of the Ihh activated transcription factor Gli2 is targeted in the growth plate. Furthermore, Gli2 overexpressing mice also carrying a p53 deficiency develop larger more cellular cartilage lesions, but do not develop chondrosarcoma. Embryonic growth plates of Gli2 transgenic and p53 KO mice showed decreased apoptosis compared to WT, with an enhanced effect observed in the double transgenic mice. Furthermore, a microarray screen of C2C12 cells with increased Hh signaling showed a downregulation of IGFBP-3 (insulin-like growth factor binding protein-3), a p53 target gene with known anti-apoptotic effects in other tumor cell models.

To investigate whether IGFBP-3 is regulated by Hh/Gli and p53 signaling pathways in growth plate development and maintenance, murine limb explants were treated with Shh and/or IGFBP-3 peptides. Treatment of these limbs with Shh reduced apoptosis, similar to the effect observed in p53 KO mice, of which addition of IGFBP-3 rescued their apoptotic deficient phenotype. Moreover, ChIP analysis of human CSA samples revealed a Gli2 transcription factor binding site upstream of IGFBP-3, suggesting that Hh signaling directly regulates IGFBP-3 expression within the growth plate. This was confirmed by decreased luciferase activity following activation of the Hh pathway in cell lines transfected with an IGFBP-3 promoter construct, but was not observed when transfected with a mutated construct of the putative Gli binding site. Finally, mice expressing Gli2 developed substantially fewer tumors when they were also deficient for Igf2.

Overall our data suggests that the combined effects of Gli2 overexpression and p53 deficiency act to inhibit IGFBP-3, resulting in decreased apoptosis and the development of large cartilage lesions observed in adult murine limbs. Therefore, IGF signaling-meditated apoptosis may play a major role in regulating the progression of benign enchondroma to malignant chondrosarcoma.

CURRICULUM VITAE

Education

2005-present Ph.D. University of Toronto
Department of Laboratory Medicine and Pathobiology
Hospital for Sick Children
Department of Developmental and Stem Cell Biology

2000-2005 Hon. B.Sc. University of Toronto with Distinction
Major: Biology, Minor: Anthropology

Research Experience

2004–2005 Student Research Project on diuretic peptides in Rhodnius prolixus
- Dissect adult specimens and observe location of diuretic peptides in the gut and CNS using immunohistochemistry

2003 Archaeology Lab Assistant, Volunteer, University of Toronto
- Collected quantitative data on fossil groups
- Sorted fossils and artifacts into categories

Teaching Experience

2005-2006 Teaching Assistant, 2nd year undergraduate Physiology, University of Toronto
- Lab based instruction, marking of assignments and tests, exam moderation

Extracurricular Activities

2009 Executive committee, Life Science Career Day Seminars
- Graduate student-run initiative at the University of Toronto that aims to help graduate students explore the various career paths that can stem from a life sciences graduate degree

2009 Volunteer Coordinator, Heart and Stroke Foundation-University of Toronto
- Recruitment of volunteers and communication of volunteering opportunities for upcoming events

2002-2003 Finance Minister, Erindale Math Club, University of Toronto
- Raised money and communicated balance of funds

2002-2004 Intramural team member, Indoor Volleyball

Awards

2005-2009 RESTRACOMP, Hospital for Sick Children Foundation
- Awarded to graduate students in biomedical sciences by the SickKids Foundation Graduate Scholarships at the University of Toronto based on academic performance, publication activity, and other research, academic activities to cover their stipend.

2009 Gallie Day, The Department of Surgery, University of Toronto
- Awarded second place in oral presentation competition

2009 Gordon Research Conference: Cartilage Biology and Pathology
- Poster prize winner

2007 Gallie Day, The Department of Surgery, University of Toronto
- Awarded second place in poster prize competition

2005,2006 University of Toronto Fellowship Award

2000-2004 Volunteer Recognition Award

2000 University of Toronto Entrance Scholarship

Publications

1. Lin AC, Seeto BL, Bartoszko JM, Khoury MA, Whetstone H, Ho L, Hsu C, Ali AS, Alman BA. Modulating hedgehog signaling can attenuate the severity of osteoarthritis. Nat Med. 2009 Dec;15(12):1421-5. Epub 2009 Nov 15.
2. Ho L, Alman B. Protecting the Hedgerow: p53 and Hedgehog pathway interactions Cell Cycle. 2010 Feb. 1:9(3).
3. Ho L, Stojanovski A, Whetstone H, Wei QX, Mau E, Wunder JS, Alman B. Gli2 and p53 cooperate to regulate IGFBP-3- mediated chondrocyte apoptosis in the progression from benign to malignant cartilage tumors. Cancer Cell. 2009 Aug 4:16(2):126-36.

Maintenance of bone growth and bone mass requires Hedgehog signaling

Yukiko Maeda Ph.D.

Department of Developmental Biology, Harvard School of Dental Medicine, Boston, MA, USA

Indian hedgehog (Ihh) plays a crucial role during growth plate and endochondral bone formation. Our previous studies with the/col2 α 1-Cre ER*;Ihhd/d/ animals demonstrated that /Ihh/ deletion from all postnatal chondrocytes results in complete loss of the growth plate and subsequently trabecular bone (Maeda et al. 2007) .

Since the growth plate is required as a template for trabecular bone direct role of chondrocyte derived Ihh on trabecular bone formation is unknown.

Furthermore, activation of the Ihh downstream target PTH/PTHrP receptor (Jansen) could not rescue the loss of growth plate, suggesting Ihh is essential to maintain the growth plate independent of PTHrP (Maeda et al.2009) .

Therefore to further address the question whether chondrocyte-derived Ihh directly affects trabecular bone formation in postnatal life we generated a new hypomorph mouse model, /colX-Cre;Ihhd/d/, in which Ihh is only removed from a subset of hypertrophic chondrocytes.

/ColX-Cre;Ihhd/d/ mice were born with the expected Mendelian pattern of inheritance and looked indistinguishable from their normal littermates at birth. Deletion of /Ihh/ from hypertrophic chondrocytes was confirmed by qRT-PCR and /in situ/ hybridization. We analyzed control and mutant mice at 3 weeks and 4 months and could demonstrate that a growth plate as preserved. Micro CT analysis and TRAP staining of bone from /colX-Cre;Ihhd/d /mice showed reduced bone volume and increased osteoclast number when compared to their control littermates at postnatal 3 weeks and 4 months. These results suggest that chondrocyte-derived Ihh signaling is required for maintenance of postnatal bone.

A. Positions and Honors

Research Positions:

2004-present	Research Associate, Department of Developmental Biology, Harvard School of Dental Medicine, Boston, M
2004	PhD Student, Center of Excellence Fellow (Super Student) at 21 Century COE Program, Laboratory of M. Noda, Dept. of Molecular Pharmacology, Tokyo Medical and Dental University, Tokyo, Japan
2000-2004	PhD Student, Laboratory of M. Noda, Dept. of Molecular Pharmacology, Tokyo Medical and Dental University, Tokyo, Japan

B. Selected Peer-reviewed Publications

1. Correa D, Kiviranta R, Hesse E, Saito H, Yamana K, Neff L, Sitara D, Maeda Y, Warming S, Jenkins NA, Copeland NG, Lanske B, Horne, WC. Baron R. The Transcriptional Co-regulator Zfp521 Regulates Chondrocyte Proliferation and Differentiation, Contributing to the Effects of Parathyroid Hormone-Related Peptide (PTHrP) on the Growth Plate. Dev Cell (Under revision)
2. Maeda Y, Schipani E, Densmore JM Lanske B, Partial rescue of postnatal growth plate abnormalities in Ihh mutants by expression of a constitutively active PTH/PTHrP receptor. Bone (In press)
3. Ochiai T, Shibukawa Y, Nagayama M, Munday C, Yasuda T, Okabe T, Shimono K, Iwamoto M, Hasegawa T, Maeda Y, Lanske B, Pacifici M, Koyama E, Indian hedgehog roles in postnatal TMJ development and organization. J Dent Res (in Press)
4. Maeda Y, Nakamura E, Nguyen MT, Suva LJ, Swain FL, Razzaque MS, Mackem S, Lanske B, Indian Hedgehog produced by postnatal chondrocytes is essential for maintaining a growth plate and trabecular bone. PNAS. 2007 104 (15) :6382-7.
5. Koyama E, Young B, Shibukawa Y, Nagayama M, Enomoto IM, Iwamoto M, Maeda Y, Lanske B, Song B, Serra R, Pacifici M, Conditional Kif3a ablation causes abnormal hedgehog signaling topography, growth plate dysfunction and ectopic cartilage formation in mouse cranial base synchondroses. Development 2007 134 (11) :2159-69.
6. Matsumoto K, Nishihara S, Kamimura M, Shiraishi T, Otoguro T, Uehara M, Maeda Y, Ogura K, Lumsden A, Ogura T, The prepattern transcription factor Irx2, a target of the FGF8/MAP kinase cascade, is involved in cerebellum formation. Nat Neurosci. 2004 7 (6) :605-12.
7. Kida Y, Maeda Y, Shiraishi T, Suzuki T, Ogura T, Chick Dach1 interacts with the Smad complex and Sin3a to control AER formation and limb development along the proximodistal axis. Development 2004 131 (17) :4179-87.
8. Ohyama Y, Nifuji A, Maeda Y, Amagasa T, Noda M., Spaciotemporal association and bone morphogenetic protein regulation of sclerostin and osterix expression during embryonic osteogenesis. Endocrinology 2004 145 (10) :4685-92.
9. Maeda Y, Tsuji K, Benezra R, Nifuji A, Noda M, Inhibitory helix-loop-helix transcription factors Id1/Id3 are required for bone formation in vivo. J Cell Biochem. 2004 1;93 (2) :337-44.
10. Maeda Y and Noda M, Coordinated development of embryonic long bone on chorioallantoic membrane in ovo prevents perichondrium-derived suppressive signals against cartilage growth. Bone 2003 32 (1) :27-34
11. Noda M, Kashimada K, Takamoto M, Yumoto K, Maeda Y, Usui M, Ishijima M. The meaning of phosphate in bone formation Clin Calcium 2001 Oct;11 (10) :1315- 20. Japanese.

C. Meetings and Presentations

1. ASBMR Meeting (Poster) Denver, CO (2009) "Indian hedgehog expressed from hypertrophic chondrocytes is essential for adult trabecular bone formation."
2. ASBMR Meeting (Oral) Montreal, QC (2008) "Chondrocyte-derived Ihh Is Required for Osteoblast Differentiation Despite Reconstitution of a Normal Growth Plate"
3. ASBMR Meeting (Poster) Honolulu, HI (2007) "Indian Hedgehog Is Essential for Postnatal Bone"
4. ASBMR Meeting (Oral) Philadelphia, PA (2006) "Indian Hedgehog (Ihh) Is Required for Endochondral Bone Formation after Birth"
5. Sun Valley Workshop, (Oral) Sun Valley, ID (2006) " Indian hedgehog is required for endochondral bone formation after birth"
6. ASBMR Meeting (Plenary Poster) Nashville, TN (2005) "Chondrocyte-Specific Deletion of Indian Hedgehog (Ihh) in Postnatal Life"
7. IBMS Meeting (Oral) Osaka, Japan (2003) "In vivo bone formation induced by BMP injections onto calvaria and angiogenesis during fracture healing are impaired in Id1/Id3 double gene knockout mice"
8. ASBMR Meeting (Poster) Minneapolis, MN (2003) "Limbin, a gene required for normal lengthening of limbs, is expressed in chondrocytes in culture and its levels are down-regulated by BMP2"
9. ASBMR Meeting (Oral) San Antonio, TX (2002) "Id1/Id3 double gene knockout results in defects in angiogenesis in fracture callus and suture development"
10. IBMS Meeting (Poster) Okayama, Japan (2002) "The growth suppression of epiphyseal cartilage by perichondrium is blocked in in ovo organ culture system"

11. ASBMR Meeting (Poster) Phenix, AL (2001)
"Perichondrium acts as an inducer of apoptosis in epiphyseal chondrocytes in in vitro organ cultures but its inhibitory activity is blocked in in ovo organ cultures"
12. JBS Meeting (Poster) Yokohama, Japan (2000)
"The interaction between angiogenesis and perichondrium during endochondral bone formation"
13. MBSJ Meeting (Poster) Hukuoka, Japan (1999)
"The role of chicken Dachshund gene during neural development"

D. Awards and Honors

2007 Dean's Scholars Award, Harvard School of Dental Medicine
"Indian Hedgehog produced by postnatal chondrocytes is essential for maintaining a growth plate and trabecular bone"

2006 Dean's Scholars Award, Harvard School of Dental Medicine
"The role of Indian hedgehog in endochondral bone formation after birth"

2006 ASBMR Harold M. Frost Young Investigator Award, 36th International Sun Valley Workshop on Skeletal Tissue Biology
"Indian hedgehog is required for endochondral bone formation after birth"

2006 ASBMR Young Investigator Award, American Society for Bone and Mineral Research (ASBMR) , Philadelphia
"Indian Hedgehog (Ihh) Is Required for Endochondral Bone Formation after Birth"

2003 Travel Award for International Bone and Mineral Society (IBMS)
"In vivo bone formation induced by BMP injections onto calvaria and angiogenesis during fracture healing are impaired in Id1/Id3 double gene knockout mice"

2003 21st Century COE Program, Super Student award, Tokyo Medical and Dental University
"Functional analysis of chondrodysplasia causative gene LIMBIN (LBN)"

E. Teaching

2004-present Teaching to graduate and undergraduate students, Harvard School of Dental Medicine, Boston, MA

2000-2004 Teaching assistant of undergraduate students, Tokyo Medical and Dental University, Tokyo, Japan