Tokyo Medical and Dental University
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卓越した大学院拠点形成支援補助金
国際シンポジウム

Molecular mechanism in bone and tooth, its clinical implication

東京医科歯科大学

歯・骨関連疾患のグローバル研究センター国際シンポジウム

February 17th~18th, 2014
Tokyo Medical and Dental University

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2014.2.17 (Mon)

9 : 00 − 9 : 10 President Address
Takashi Ohyama

Opening remark
Atsushi Okawa

Session 1 Chairpersons : Bjorn R. Olsen, Atsushi Okawa

9 : 10 − 10 : 25 **Henry M. Kronenberg**
Flexibility in the osteoblast lineage

10 : 25 − 11 : 40 **Shu Takeda**
Control of bone metabolism via organ crosstalk

Session 2 Chairpersons : Benjamin A. Alman, Shohei Kasugai

12 : 30 − 13 : 45 **Akira Yamaguchi**
Bone destruction by oral cancer

13 : 45 − 15 : 00 **Hiroshi Takayanagi**
Forefront of osteoimmunology

15 : 00 − 15 : 30 Poster Session, Coffee Break

Session 3 Chairpersons : Ichiro Nishimura, Ichiro Sekiya

15 : 30 − 16 : 45 **Vicki Rosen**
Regenerative potential of the knee meniscus

16 : 45 − 18 : 00 **Hiroshi Asahara**
Combinatorial approach to identify gene regulation of inflammatory signals at RNA level

18 : 30 − Reception

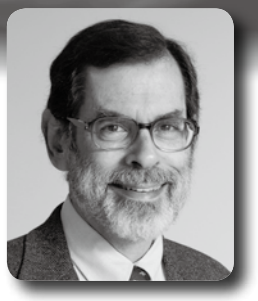
2014.2.18（Tue）

Session 4	**Chairpersons : Henry M. Kronenberg, Keiji Moriyama**
9：00 − 10：15	**Bjorn R. Olsen** Craniofacial dysmorphogenesis and infantile hemangioma – the antrax toxin receptor connection
10：15 − 11：30	**Ichiro Sekiya** Cartilage and meniscus regeneration with synovial stem cells

Session 5	**Chairpersons : Vicki Rosen, Takeshi Muneta**
12：20 − 13：35	**Benjamin A. Alman** Fracture repair and beta-catenin in aging and disease : implications for an approach to therapy
13：35 − 14：50	**Ichiro Nishimura** Osteoclast as MDSC (myeloid-derived suppressor cell) and its role in ONJ and tumor bone metastasis
14：50 − 14：55	Closing Remark **Atsushi Okawa**

C O N T E N T S

Flexibility in the osteoblast lineage



Henry M. Kronenberg, M.D.

Professor and Director
Endocrine Unit, Massachusetts General Hospital and
Harvard Medical School

The classic view, based primarily on studies of cells in culture, is that mesenchymal progenitors in the bone marrow (called "mesenchymal stem cells" by some investigators) have the potential to differentiate into osteoblasts, chondrocytes, and adipocytes. Osteoblast precursors first express Runx2, then osterix, and then other transcription factors that direct these cells first to proliferate and then differentiate into mature osteoblasts. The fates of osteoblasts include their dying by apoptosis or, instead, becoming osteocytes or inactive bone lining cells. In vivo studies using cre recombinase, controlled by various promoters and sometimes requiring tamoxifen administration for activation (through activation of a cre recombinase linked to the ligand binding domain of a mutated estrogen receptor) (creERt), have allowed the marking and genetic manipulation of cells in the skeletal system at various stages of differentiation and at specific times. These studies have demonstrated unanticipated flexibility in the lineage program just outlined.

Here we will show that, after osteoblast precursors express osterix in vivo in mice, removal of β-catenin expression from these cells steers many of these pre-osteoblasts into the adipocyte lineage. We also show that many osterix-expressing cells become stromal cells that support hematopoiesis. Further we show that inactive bone lining cells can be reactivated to participate in bone formation as mature osteoblasts after PTH administration. Finally, we show that collagen II-creERt can mark stem cells that subsequently can become osteoblasts, chondrocytes, or adipocytes and continue to do so for months after one administration of tamoxifen. This promoter can be activated by tamoxifen to generate marked osteoblasts several months after birth. When PTH is given to these mice, the number of osteoblast precursors increases in the several days after PTH administration, as indicated by counting of the cells marked as expressing the collagen II promoter. Thus, both the number and the fate of early cells of the osteoblast lineage can be manipulated to serve the changing needs of the organism.

CURRICULUM VITAE

Education

1962-1966 B.A. History and Literature Harvard College
1966-1970 M.D. Medicine Columbia University

Position

1984-1997 Director, Endocrine Clinical Laboratories Massachusetts General Hospital
1985- Medical Administrative Committee Massachusetts General Hospital
1985-1987 Interim Chief, Thyroid Unit Massachusetts General Hospital
1986-1989 Director, Endocrine Division Massachusetts General Hospital
1997-2000 Co-Chair, Academic Council, Department of Medicine Massachusetts General Hospital
1998-2007 Director, Endocrine Division Massachusetts General Hospital
2007 Chair, Cartilage Biology and Pathology Conference Gordon Research Conferences
2009-2010 Director, Endocrine Division Massachusetts General Hospital
2013- Director, Endocrine Division Massachusetts General Hospital

Award and Honors

2000 Van Wyck Lectureship University of North Carolina
2002 R.L. Creuss Lecturer McGill University, Montreal
2002 Novartis Lecturer Canadian Society of Endocrinology & Metabolism
2002 5th Annual John G. Haddad, Jr Distinguished Memorial Lecturer
University of Pennsylvania School of Medicine
2003 Transoceanic Lecture Prize
European Federation of Endocrine Societies
2003 William F. Neuman Award
The American Society for Bone and Mineral Research (ASBMR)
2006 Louis V. Avioli Memorial Lecturer
The American Society for Bone and Mineral Research (ASBMR)
2011 Michael & Irene Karl Visiting Professor
Washington University School of Medicine
2011 2nd Iain MacIntyre Memorial Lecturer
4th New York Skeletal Biology and Medicine Conference
2011 Gideon A. Rodan Award for Excellence in Mentoring
The American Society for Bone and Mineral Research (ASBMR)
2012 The Ninth Torsten N. Wiesel Distinguished Lecturer
Hospital for Special Surgery, New York, New York
2012 Triennial International Prize
Austrian Bone and Mineral Society
2013 John Baxter Memorial Lecturer

Publications

1. Kobayashi T, Lu J, Cobb BS, Rodda SJ, Mcmahon AP, Schipani E, Merkenschlager M, Kronenberg, HM. Dicer-dependent pathways regulate chondrocyte proliferation and differentiation. PNAS 2008, 105:1949-1954. PMCID: PMC2538863
2. Mak KK, Kronenberg HM, Chuang PT, Mackem S, Yang Y. Indian hedgehog signals independently of PTHrP to promote chondrocyte hypertrophy. Development 2008; 135:1947-56.
3. Ono N, Nakashima K, Rittling SR, Schipani E, Hayata T, Ezura Y, Soma K, Denhardt DT, Kronenberg HM, Noda M. Osteopontin negatively regulates parathyroid hormone receptor signaling in osteoblasts. JBC 2008;283:19400-19409.
4. Provot S, Nachtrab G, Paruch J, Chen AP, Silva A, Kronenberg HM. A-Raf and B-Raf are dispensable for normal endochondral bone development and PTHrP suppresses ERK activation in hypertrophic chondrocytes. Mol Cell Biol. 2008;28:344-357. PMCID: PMC2223319
5. Wu JY, Purton LE, Rodda S, Chen M, Weinstein LS, McMahon AP, Scadden DT, Kronenberg HM. Osteoblastic regulation of B lymphopoiesis is mediated by Gsx03B1-dependent signaling pathways. PNAS 2008;105:16976-16981. PMCID: PMC2579363
6. Adams GB, Alley IR, Chug UI, Chabner KT, Jeanson NT, Lo Celso C, Marsters ES, Chen M, Weinstein LS, Lin CP, Kronenberg HM, Scadden DT. Haematopoietic stem cells depend on Galpha(s)-mediated signaling to engraft bone marrow. Nature 2009;459(7243):103-7. PMCID: PMC2761017
7. Bai XH, Wang DW, Kong L, Zhang Y, Luan Y, Kobayashi T, Kronenberg H, Yu XP, Liu CJ. ADAMTS-7, a direct target of PTHrP, adversely regulates endochondral bone growth by associating with and inactivating GEP growth factor. Mol Cell Biol 2009;29(15)4201-19. PMCID: PMC2715794
8. Conen KL, Nishimori S, Provot S, Kronenberg HM. The transcriptional cofactor Lbh regulates angiogenesis and endochondral bone formation during fetal bone development. Dev Biol 2009
2009;332(2):348-58. PMCID: PMC2760734
9. Miclea RL, Karperien M, Bosch CAJ, van der Horst G, van der Valk MA, Kobayashi T, Kronenberg HM, Rawadi G, Akcakaya P, Lowik CWGM, Fodde R, Wit J-M, Robanus-Maandag ECR. Adenomatous pilyposis coli-mediated control of beta-catenin is essential for both chondrogenic and osteogenic differentiation of skeletal precursors. BMC Developmental Biology 2009; 9:26. PMCID: PMC2678105
10. Terauchi M, Li J-Y, Bedi B, Baek K-H, Tawfeek H, Galley S, Gilbert L, Nanes MS, Zayzafoon M, Guldberg R, Lamar DL, Singer MA, Lane TF, Kronenberg HM, Weitzmann MN, Pacifici R. T lymphocytes amplify the anabolic activity of parathyroid hormone through Wnt 10b signaling. Cell Metab 2009;10(3):229-40. PMCID: PMC2761855
11. Guo J, Liu M, Yang D, Bouxsein ML, Saito H, Galvin RJS, Kuhstoss SA, Thomas CC, Schipani E, Baron R, Bringhurst

FR, Kronenberg HM. Suppression of Wnt signaling by DKK1 attenuates PTH-mediated stromal cell response and new bone formation. Cell Metabolism 2010;11:161-71. PMCID: PMC2819982.

12. Kamiya N, Kobayashi T, Mochida Y, Yu P, Yamauchi M, Kronenberg H, Mishina Y. Wnt inhibitors Dkk1 and Sost are downstream targets of BMP signaling through the Type 1A receptor (BMPR1A) in osteoblasts. JBMR 2010:25(2);200-10. PMCID: PMC3153381
13. Guo J, Liu M, Yang D, Bouxsein ML, Thomas CC, Schipani E, Bringhurst FR, Kronenberg HM. Phospholipase C signaling via the PTH/PTHrP receptor is essential for normal bone modeling and remodeling. Endocrinology 2010;151:3502-13. PMCID: PMC2940537
14. Maes C, Kobayashi T, Selig MK, Torrekens S, Roth SI, Mackem S, Carmeliet G, Kronenberg HM. Osterix-expressing immature osteoblast precursors invade growth cartilage along with blood vessels. Developmental Cell 2010;19:329-44.
15. Tawfeek H, Bedi B, Li J-Y, Adams J, Kobayashi T, Weitzmann MN, Kronenberg HM, pacifici R. Disruption of PTH receptor 1 in T cells protects against PTH-induced bone loss. PLoS One. 2010;5(8):e12290. Published online 2010 August. PMCID: PMC2924900
16. Hirai T, Chagin A, Kobayashi T, Mackem S, Kronenberg H. PTH/PTHrP receptor signaling is required for maintenance of the growth plate in postnatal life. PNAS 2011;108(1):191-6. PMCID: PMC3017151
17. Moisan A, Rivera MN, Lotinun S, Akhavanford S, Coffman EJ, Cook EB, Stoykova S, Mukherjee S, Schoonmaker JA, Burger A, Kim WJ, Kronenberg HM, Baron R, Haber DA, Bardeesy N. The WTX tumor suppressor regulates mesenchymal progenitor cell fate specification. Dev Cell 2011;20(5):583-96.
18. Morishita M, Ono N, Miyai K, Nakagawa T, Hanyu R, Nagao M, Kamoiratanakul P, Notomi T, Rittling SR, Denhardt DT, Kronenberg HM, Ezura Y, Hayata T, Nakamoto T, Noda M. Osteopontin deficiency enhances parathyroid hormone/parathyroid hormone related peptide receptor (PPR) signaling-induced alteration in tooth formation and odontoblastic morphology. Tissue Cell 2011;43(3):196-200.
19. Ono N, Nakashima K, Schipani E, Hayata T, Ezura Y, Soma K, Kronenberg HM, Noda M. Constitutively active PTH/PTHrP receptor specifically expressed in osteoblasts enhances bone formation induced by bone marrow ablation. J Cell Pysiol 2011. Doi:10.1002/jcp22986 [Epub ahead of print]. PMID21866553
20. Wu JY, Aarnisalo P, Bastepe M, Sinha P, Fulzele K, Selig MK, Chen M, Poulton IJ, Purton LE, Sims NA, Weinstein LS, Kronenberg HM. Gsα enhances commitment of mesenchymal progenitors to the osteoblast lineage but restrains osteoblast differentiation in mice. J Clin Invest 2011:121(9):3492-504. PMCID: PMC3163961
21. Hanyu R, Wehbi VL, Hayata T, Moriya S, Feinstein TN, Ezura Y, Nagao M, Saita Y, Hemmi H, Notomi T, Nakamoto T, Schipani E, Takeda S, Kaneko K, Kurosawa H, Karsenty G, Kronenberg HM, Vilardaga JP, Noda M. Anabolic action of parathyroid hormone regulated by the β2-adrenergic receptor. Proc Natl Acad Sci USA 2012;109(19):7433-8.
22. Kim SW, Pajevic PD, Selig M, Barry KJ, Yang JY, Shin CS, Baek WY, Kim JE, Kronenberg HM. Intermittent PTH administration converts quiescent lining cells to active osteoblasts. J Bone Miner Res. 2012 may 23 [Epub ahead of print].
23. Ohishi M, Ono W, Ono N, Khatri R, Marzia M, Baker EK, Root SH, Wilson TL, Iwamoto Y, Kronenberg HM, Aguila HL, Purton LE, Schipani E. A novel population of cells expressing both hematopoietic and mesenchymal markers is present in the normal adult bone marrow and is augmented in a murine model of marrow fibrosis. Am J Pathol. 2012;180(2):811-8. Epub 2011 Dec 5.
24. Ono N, Nakashima K, Schipani E, Hayata T, Ezura Y, Soma K, Kronenberg HM, Noda M. Constitutively active PTH/PTHrP receptor specifically expressed in osteoblasts enhances bone formation induced by bone marrow ablation. J Cell Physiol. 2012;227(2):408-15.
25. Park D, Spencer JA, KohBI, Kobayashi T, Fujisaki J, Clemens TL, Lin CP, Kronenberg HM, Scadden DT. Endogenous bone marrow MSCs are dynamic, fate-restricted participants in bone maintenance and regeneration. Cell Stem Cell 2012;10(3):259-72.
26. Song L, Liu M, Ono N, Bringhurst FR, Kronenberg HM, Guo J. Lost of wnt/β-catenin signaling causes cell fate shift of preosteoblasts from osteoblasts to adipocytes. J Bone Miner Res. 2012;27(11):2344-58.
27. Fulzele K, Krause DS, Panaroni C, Saini V, Barry KJ, Liu X, Lotinun S, Baron R, Bonewald L, Feng JQ, Chen M, Weinstein LS, Wu JY, Kronenberg HM, Scadden DT, Divieti Pajevic P. Myelopoiesis is regulated by osteocytes through Gsα -dependent signaling. Blood 2013; 121(6):930-9.
28. Guo J, Song L, Liu M, Segawa H, Miyamoto K, Bringhurst FR, Kronenberg HM, Jüppner H. Activation of a Non-cAMP/PKA signaling pathway downstream of the PTH/PTHrP receptor is essential for a sustained hypophosphatemic response to PTH infusion in male mice. Endocrinology 2013;53(2):487-96.
29. Pozzi S, Fulciniti M, Yan H, Vallet S, Homare E, Patel K, Santo L, Cirstea D, Hideshima T, Schirtzinge L, Kuhstoss S, Anderson KC, Munshi N, Scadden D, Kronenberg HM, Raje N. In vivo and in vitro effects of a novel anti-Dkk1 neutralizing antibody in multiple myeloma. Bone 2013;53:487-496.

MEMO

Control of bone metabolism via organ crosstalk

Shu Takeda, M.D., Ph.D.

Professor
Department of Physiology and Cell Biology, Graduate School of
Medical and Dental Sciences, Tokyo Medical and Dental University

It was believed that cytokines and hormones are main regulators of bone remodeling. However, this view has been challenged. Organ network has been shown to play a major role in homeostasis, recently. Bone is not the exception.

Clinically, it is well known that head trauma accelerates fracture healing. Advances in molecular genetics revealed that neurons and neuropeptides, including sympathetic nervous system, are intimately involved in bone remodeling.

Semaphorin 3A (Sema3A) is a diffusible axonal chemorepellent that plays an important role in axon guidance. Previous studies have demonstrated that Sema3A is an osteo-anabolic autocrine and, accordingly, Sema3A-KO mice develop a low bone mass due to decreased bone formation. However, recently, we demonstrated that osteoblast-specific Sema3A-KO mice had normal bone mass, even though the expression of Sema3A in bone was substantially decreased. In contrast, mice lacking Sema3A in neurons had low bone mass similar to Sema3A-KO mice, indicating that neuron-derived Sema3A is responsible for the bone abnormalities independent of the local effect of Sema3A in bone. Indeed, sensory innervations of trabecular bone were significantly decreased in neuron-specific Sema3A-KO. Moreover, ablating sensory nerves decreased bone mass in wild-type mice, whereas it did not deteriorate low bone mass phenotype in neuron specific Sema3A-KO mice, further indicating the essential role of sensory nervous system in normal bone homeostasis. Thus, we demonstrated that sensory nervous system is also a critical regulator of bone remodeling.

In this lecture, I would like to discuss novel regulators of bone remodeling.

CURRICULUM VITAE

Education

1992 M.D. University of Tokyo, School of Medicine
2002 Ph.D. University of Tokyo, Graduate School of Medicine

Position

1999 Postdoctral Fellow, Baylor College of Medicine, Houston
2003 Clinical Fellow, Dept of Endocrinorogy and Metabolism Mishuku Hospital, Tokyo
2004 Associate Professor（Junior）, Department of Orthopaedic Surgery, 21 Center of Excellence Program, Graduate School, Tokyo Medical and Dental University
2005-2008 Associate Professor（Senior）, Department of Orthopaedic Surgery, 21 Center of Excellence Program, Graduate School, Tokyo Medical and Dental University
2008 Associate Professor, Department of Orthopaedic Surgery, 21 Center of Excellence Program, Graduate School, Tokyo Medical and Dental University
2009- Associate Professor, Associate Professor, Section of Nephrology, Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Keio University
2013-present Professor, Dept. of Physiology and Cell Biology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University
2013-present Principle Investigator, CREST, Japan Science and Technology Agency

Award and Honors

1997 President Book Award of American Society for Bone and Mineral Research
1997 Young Investigator Award of Japanese Society for Bone and Mineral Metabolism
2000 Young Investigator Award of American Society for Bone and Mineral Research
2007 Corresponding author for the presentation: Most Outstanding Abstract Award for the 29th American Society for Bone and Mineral Research annual meeting
2008 Research Award of Japanese Society for Bone and Mineral Metabolism
2010 Research Award of Japanese Endocrine Society
2011 Japan Society for the Promotion of Science Prize
2011 Best Reviewer of "Bone"
2012 Academic Award of Japanese Society for Bone and Mineral Metabolism
2013 Member of the American Society for Clinical Investigation

Publications

1. Elefteriou, F., J.D. Ahn, S. Takeda, M. Starbuck, X. Yang, X. Liu, H. Kondo, W.G. Richards, T.W. Bannon, M. Noda, K. Clement, C. Vaisse, and G. Karsenty 2005 Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature 434*:514-20.
2. Fukushima, N., R. Hanada, H. Teranishi, Y. Fukue, T. Tachibana, H. Ishikawa, S. Takeda, Y. Takeuchi, S. Fukumoto, K. Kangawa, K. Nagata, and M. Kojima 2005 Ghrelin directly regulates bone formation. *J Bone Miner Res 20*:790-8.
3. Kondo, H., A. Nifuji, S. Takeda, Y. Ezura, S.R. Rittling, D.T. Denhardt, K. Nakashima, G. Karsenty, and M. Noda 2005 Unloading induces osteoblastic cell suppression and osteoclastic cell activation to lead to bone loss via sympathetic nervous system. *J Biol Chem 280*:30192-200.
4. Takeda, S. 2005 Central control of bone remodeling. *Biochem Biophys Res Commun 328*:697-9.
5. Kamekura, S., Y. Kawasaki, K. Hoshi, T. Shimoaka, H. Chikuda, Z. Maruyama, T. Komori, S. Sato, S. Takeda, G. Karsenty, K. Nakamura, U.I. Chung, and H. Kawaguchi 2006 Contribution of runt-related transcription factor 2 to the pathogenesis of osteoarthritis in mice after induction of knee joint instability. *Arthritis Rheum 54*:2462-70.
6. Ito, N., S. Fukumoto, Y. Takeuchi, S. Takeda, H. Suzuki, T. Yamashita, and T. Fujita 2007 Effect of acute changes of serum phosphate on fibroblast growth factor (FGF)23 levels in humans. *J Bone Miner Metab 25*:419-22.
7. Nakamura, T., Y. Imai, T. Matsumoto, S. Sato, K. Takeuchi, K. Igarashi, Y. Harada, Y. Azuma, A. Krust, Y. Yamamoto, H. Nishina, S. Takeda, H. Takayanagi, D. Metzger, J. Kanno, K. Takaoka, T.J. Martin, P. Chambon, and S. Kato 2007 Estrogen prevents bone loss via estrogen receptor alpha and induction of Fas ligand in osteoclasts. *Cell 130*:811-23.
8. Okuda, N., S. Takeda, K. Shinomiya, T. Muneta, S. Itoh, M. Noda, and Y. Asou 2007 ED-71, a novel vitamin D analog, promotes bone formation and angiogenesis and inhibits bone resorption after bone marrow ablation. *Bone 40*:281-92.
9. Sato, S., R. Hanada, A. Kimura, T. Abe, T. Matsumoto, M. Iwasaki, H. Inose, T. Ida, M. Mieda, Y. Takeuchi, S. Fukumoto, T. Fujita, S. Kato, K. Kangawa, M. Kojima, K. Shinomiya, and S. Takeda 2007 Central control of bone remodeling by neuromedin U. *Nat Med 13*:1234-40.
10. Takeda, S., *Leptin and bone*, in *Leptin*, M.C. Henson, et al., Editors. 2007, Springer. p. 1059-1068.
11. Nojiri, Y., S. Takeda, M. Enomoto, H. Nishitsuji, T. Masuda, S. Sotome, and K. Shinomiya 2008 Co-overexpression of GDNF and GFRalpha1 induces neural differentiation in neural progenitor cells in comparison to bone marrow stromal cells. *J Med Dent Sci 55*:121-8.
12. Sato, S., A. Kimura, J. Ozdemir, Y. Asou, M. Miyazaki, T. Jinno, K. Ae, X. Liu, M. Osaki, Y. Takeuchi, S. Fukumoto, H. Kawaguchi, H. Haro, K. Shinomiya, G. Karsenty, and S. Takeda 2008 The distinct role of the Runx proteins

in chondrocyte differentiation and intervertebral disc degeneration: Findings in murine models and in human disease. *Arthritis Rheum 58*:2764-75.
13. Takeda, S. 2008 Central control of bone remodelling. *J Neuroendocrinol 20*:802-7.
14. Takeda, S. and P. Ducy, *Regulation of Bone Remodeling by Central and Peripheral Nervous Signals*, in *Principle of Bone Biology*, J.P. Bilezikian, L.G. Raisz, and T.J. Martin, Editors. 2008, Elsevier. p. 1059-1068.
15. Takeda, S. and G. Karsenty 2008 Molecular bases of the sympathetic regulation of bone mass. *Bone 42*:837-40.
16. Tominaga, H., S. Maeda, M. Hayashi, S. Takeda, S. Akira, S. Komiya, T. Nakamura, H. Akiyama, and T. Imamura 2008 CCAAT/Enhancer-binding Protein {beta} Promotes Osteoblast Differentiation by Enhancing Runx2 Activity with ATF4. *Mol. Biol. Cell 19*:5373-5386.
17. Inose, H., H. Ochi, A. Kimura, K. Fujita, R. Xu, S. Sato, M. Iwasaki, S. Sunamura, Y. Takeuchi, S. Fukumoto, K. Saito, T. Nakamura, H. Siomi, H. Ito, Y. Arai, K.-i. Shinomiya, and S. Takeda 2009 A microRNA regulatory mechanism of osteoblast differentiation. *Proc Natl Acad Sci U S A 106*:20794-20799.
18. Suzuki, D., A. Yamada, T. Amano, R. Yasuhara, A. Kimura, M. Sakahara, N. Tsumaki, S. Takeda, M. Tamura, M. Nakamura, N. Wada, T. Nohno, T. Shiroishi, A. Aiba, and R. Kamijo 2009 Essential mesenchymal role of small GTPase Rac1 in interdigital programmed cell death during limb development. *Dev Biol 335*:396-406.
19. Takeda, S. 2009 Osteoporosis: A neuroskeletal disease? *Int J Biochem Cell Biol 41*:455-9.
20. Itoh, T., S. Takeda, and Y. Akao 2010 MicroRNA-208 modulates BMP-2-stimulated mouse preosteoblast differentiation by directly targeting V-ets erythroblastosis virus E26 oncogene homolog 1. *J Biol Chem 285*:27745-52.
21. Kimura, A., H. Inose, F. Yano, K. Fujita, T. Ikeda, S. Sato, M. Iwasaki, T. Jinno, K. Ae, S. Fukumoto, Y. Takeuchi, H. Itoh, T. Imamura, H. Kawaguchi, U.I. Chung, J.F. Martin, S. Iseki, K. Shinomiya, and S. Takeda 2010 Runx1 and Runx2 cooperate during sternal morphogenesis. *Development 137*:1159-67.
22. Nishikawa, K., T. Nakashima, S. Takeda, M. Isogai, M. Hamada, A. Kimura, T. Kodama, A. Yamaguchi, M.J. Owen, S. Takahashi, and H. Takayanagi 2010 Maf promotes osteoblast differentiation in mice by mediating the age-related switch in mesenchymal cell differentiation. *J Clin Invest 120*:3455-65.
23. Sato, T., D. Chida, T. Iwaya, M. Usui, M. Hatori, T. Abe, S. Takeda, and T. Yoda 2010 Non-neuronal regulation and repertoire of cholinergic receptors in organs. *BioMolecular Concepts in press*.
24. Takeda, S., *Skeletal Regulation of Energy Metabolism*, in *Bone and Development in Topic in Bone Biology*, F. Bronner, H. Roach, and M. Farach-Carson, Editors. 2010, Springer. p. 267-278.
25. Tanaka, M., T. Suganami, S. Sugita, Y. Shimoda, M. Kasahara, S. Aoe, M. Takeya, S. Takeda, Y. Kamei, and Y. Ogawa 2010 Role of central leptin signaling in renal macrophage infiltration. *Endocr J 57*:61-72.
26. Meguro, S., M. Tomita, T. Katsuki, K. Kato, H. Oh, A. Ainai, R. Ito, S. Takeda, T. Kawai, Y. Atsumi, H. Itoh, and H. Hasegawa 2011 Plasma 25-hydroxyvitamin d is independently associated with hemoglobin concentration in male subjects with type 2 diabetes mellitus. *Int J Endocrinol 2011*:362981.
27. Nagao, M., T.N. Feinstein, Y. Ezura, T. Hayata, T. Notomi, Y. Saita, R. Hanyu, H. Hemmi, Y. Izu, S. Takeda, K. Wang, S. Rittling, T. Nakamoto, K. Kaneko, H. Kurosawa, G. Karsenty, D.T. Denhardt, J.-P. Vilardaga, and M. Noda 2011 Sympathetic control of bone mass regulated by osteopontin. *Proceedings of the National Academy of Sciences*.
28. Ogata, N., Y. Shinoda, N. Wettschureck, S. Offermanns, S. Takeda, K. Nakamura, G.V. Segre, U.-i. Chung, and H. Kawaguchi 2011 Gαq Signal in Osteoblasts Is Inhibitory to the Osteoanabolic Action of Parathyroid Hormone. *Journal of Biological Chemistry 286*:13733-13740.
29. Hinoi, E., Ochi, H., Takarada, T., Nakatani, E., Iezaki, T., Nakajima, H., Fujita, H., Takahata, Y., Hidano, S., Kobayashi, T., Takeda, S., and Yoneda, Y. Positive regulation of osteoclastic differentiation by growth differentiation factor 15 upregulated in osteocytic cells under hypoxia. *J Bone Miner Res 27*:938-49, 2012
30. Hanyu, R., Wehbi, V.L., Hayata, T., Moriya, S., Feinstein, T.N., Ezura, Y., Nagao, M., Saita, Y., Hemmi, H., Notomi, T., Nakamoto, T., Schipani, E., Takeda, S., Kaneko, K., Kurosawa, H., Karsenty, G., Kronenberg, H.M., Vilardaga, J.-P., and Noda, M. Anabolic action of parathyroid hormone regulated by the β2-adrenergic receptor. *Proceedings of the National Academy of Sciences 109*:7433-7438, 2012
31. Fujita, K., Iwasaki, M., Ochi, H., Fukuda, T., Ma, C., Miyamoto, T., Takitani, K., Negishi-Koga, T., Sunamura, S., Kodama, T., Takayanagi, H., Tamai, H., Kato, S., Arai, H., Shinomiya, K., Itoh, H., Okawa, A., and Takeda, S. Vitamin E decreases bone mass by stimulating osteoclast fusion. *Nat Med 18*:589-594, 2012
32. Iwasaki, M., Piao, J., Kimura, A., Sato, S., Inose, H., Ochi, H., Asou, Y., Shinomiya, K., Okawa, A., and Takeda, S. Runx2 haploinsufficiency ameliorates the development of Ossification of the Posterior Longitudinal Ligament. *PLoS ONE. 7*:e43372, 2012
33. Fukuda, T., Takeda, S., Xu, R., Ochi, H., Sunamura, S., Sato, T., Shibata, S., Yoshida, Y., Gu, Z., Kimura, A., Ma, C., Xu, C., Bando, W., Fujita, K., Shinomiya, K., Hirai, T., Asou, Y., Enomoto, M., Okano, H., Okawa, A., and Itoh, H. Sema3A regulates bone-mass accrual through sensory innervations. *Nature* 2013

MEMO

Bone destruction by oral cancer

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Oral squamous cell carcinoma (OSCC) frequently invades the jaws, and this invasion is associated with a worse prognosis. The mechanism underlying the bone invasion remains poorly understood. We histopathologically investigated mandibular invasion patterns in 97 cases of primary OSCC, and showed that in all cases varying amounts of fibrous connective tissues intervened between the tumor cells and the bone. Immunohistochemistry revealed RANKL expression in the fibroblastic cells that were adjacent to the osteoclasts in the area of bone resorption. These results suggest that the fibrous stroma is involved in osteoclastic bone resorption. To explore the molecular mechanism, we conducted microarray analyses using 43 human OSCC specimens, and revealed that many of specimens overexpressed *PTHrP* mRNA, but a few overexpressed *IL-6* mRNA. Immunohistochemical analysis revealed that IL-6 was expressed not only in cancer cells but also in fibroblasts at tumor-bone interface. Conditioned media (CM) derived from the culture of oral cancer cell lines stimulated Rankl expression in stromal cells and osteoclast formation. Antibodies against both human PTHrP and mouse IL-6 receptor suppressed *Rankl* in ST2 cells and osteoclast formation induced by CM. Xenografts of OSCC cells onto the periosteal region of the parietal bone in athymic mice presented similar histology and expression profiles of RANKL and IL-6 as observed in bone-invasive human OSCC specimens. These results indicate that OSCC provides a suitable microenvironment for osteoclast formation not only by producing IL-6 and PTHrP but also by stimulating stromal cells to synthesize IL-6.

Recent reports indicated the synthesis of RANKL by OSCC cells as well as the tumor stromal cells. Indeed, HSC3 and HO-1-N-1, human OSCC cell lines, expressed *RANKL* and stimulated *Rankl* expression in UAMS-32 murine osteoblastic cell line. We discriminated the roles of RANKL synthesized by stromal cells and cancer cells in cancer-associated bone resorption by using species-specific RANKL antibodies against murine RANKL and human RANKL, respectively. Osteoclastogenesis induced by the conditioned medium of HSC3 and HO-1-N-1 cells in a co-culture of murine bone marrow cells and UAMS-32 cells was inhibited by the addition of antibodies against either mouse or human RANKL. HSC3-induced bone destruction was greatly inhibited by the administration of anti-mouse RANKL antibody in a xenograft model. HO-1-N-1-induced bone destruction was inhibited by the administration of either anti-mouse or anti-human RANKL antibody. Bone destruction induced by the transplantation of human *RANKL*-overexpressing cells (HSC3-R2) was greatly inhibited by the injection of anti-human RANKL antibody. The present study revealed that RANKL produced by both stromal and cancer cells is involved in oral cancer-induced osteoclastic bone resorption. These results provide important information for understanding the cellular and molecular basis of cancer-associated bone destruction and the mechanism of action underlying RANKL antibody (denosumab) therapy.

To explore the molecules that synthesized by OSCC cells and stimulate osteoclastic bone resorption, we established two clonal cell lines, HSC3-C13 and HSC3-C17, from the maternal oral cancer cell line, HSC3. The conditioned medium from HSC3-C13 cells showed the highest induction of *Rankl* expression in the mouse stromal cell lines ST2 and UAMS-32 as compared to that in maternal HSC3 cells and HSC3-C17 cells, which showed similar activity. The conditioned medium from HSC3-C13 cells significantly increased the number of osteoclasts in a co-culture with mouse bone marrow cells and UAMS-32 cells. Xenograft tumors generated from these clonal cell lines into the periosteal region of the parietal bone in athymic mice showed that HSC3-C13 cells caused extensive bone destruction and a significant increase in osteoclast numbers as compared to HSC3-C17 cells. Gene expression was compared between HSC3-C13 and HSC3-C17 cells by using microarray analysis, which showed that CXCL2 gene was highly expressed in HSC3-C13 cells as compared to HSC3-C17 cells. Immunohistochemical staining revealed the localization of CXCL2 in human OSS. The increase in osteoclast numbers induced by the HSC3-C13-conditioned medium was dose-dependently inhibited by addition of anti-human CXCL2-neutralizing antibody in a co-culture system. Recombinant CXCL2 increased the expression of *Rankl* in UAMS-32 cells. These results indicate that CXCL2 is involved in bone destruction induced by oral cancer. This is the first report showing the role of CXCL2 in cancer-associated bone destruction.

CURRICULUM VITAE

Education

1974 D.D.S. Tokyo Dental College
1980 Ph.D. Tokyo Medical and Dental University

Position

1980-1988 Assistant Professor, Department of Oral Pathology, School of Dentistry, Showa University
1985-1987 Visiting Assistant Professor, School of Dentistry, Washington University, Si. Loius, MO,USA
1987-1988 Visiting Assistant Professor, Orthopedic Surgery, School of Medicine, St. Louis University
1988-1998 Associate Professor, Department of Oral Pathology, School of Dentistry, Showa University
1998-2004 Professor and Chair, Department of Oral Pathology, University School of Dentistry
2004- Professor and Chair, Department of Oral Pathology Graduate School of Medical and Dental Sciences Tokyo Medical and Dental University
2011- Council member, Science Council of Japan

Award and Honors

1993 The Japanese Society for Bone and Mineral Research: Academic Award
1996 The Japanese Society of Pathology: Pathology Research Award
2005 The Japanese Pathology Award

Publications

1. Yamaguchi A, Katagiri T, Ikeda T, Wozney JM, Rosen V, Wang EA, Kahn AJ, Suda T, Yoshiki S: Recombinant human bone morphogenetic protein-2 stimulates osteoblastic maturation and inhibits myogenic differentiation in vitro. *J Cell Biol* 111:681- 687, 1991
2. Katagiri T, Yamaguchi A, Komaki M, Abe E, Takahashi N, Ikeda T, Rosen V, Wozney JM, Fujisawa-Sehara A, Suda T: Bone morphogenetic protein-2 converts the differentiation pathway of C2C12 myoblasts into the osteoblast lineage. *J Cell Biol* 127:1755-1766, 1994
3. Ishizuya T, Yokose S, Hori M, Noda T, Suda T, Yoshiki S, Yamaguchi A: Parathyroid hormone exerts disparate effects on osteoblast differentiation depending on exposure time in rat osteobllastic cells. *J Clin Invest* 99:2961-2970,1997
4. Komori T, Yagi H, Nomura S, Yamaguchi A, Sasaki K, Deguchi K, Shimuzu Y, Bronson RT, Gao Y-H, Inada M, Sato M, Okamoto R, Tominaga K, Kitamura Y, Yoshiki S, Kishimoto T: Targeted disruption of *Cbfa1* results in complete lack of bone formation owing to the maturation arrest of osteoblasts. *Cell* 89:755-764,1997
5. Kinto N, Iwamoto M, Enomoto-Iwamoto M, Noji S, Ohuchi H, Yoshida H, Kataoka H, Wada Y, Gao Y-H, Tkahashi HE, Yoshiki S, Yamaguchi A: Fibroblasts expressing Sonic hedgehog induce osteoblast differentiation and ectopic bone formation. *FEBS Letters* 404:319-323,1997
6. Yamaguchi A, Komori T, Suda T: Regulation of Osteoblast Differentiation Mediated by BMPs, Hedgehogs and Cbfa1. *Endocrine Reviews* 21:393-411,2000
7. Yuasa T, Kataoka H, Kinto N, Iwamoto M, Enomoto-Iwamoto M, Iemura S, Ueno N, Shibata Y, Kurosawa H, Yamaguchi A: Sonic hedgehog is involved in osteoblast differentiation by cooperating with BMP-2. *J Cell. Physiol* 193:225-232,2002
8. Nobta M, Tsukazaki T, Shibata Y, Chang X, Moriishi T, Sakano S, Shindo H, Yamaguchi A: Critical regulation of BMP-induced osteoblastic differentiation by Delta1/Jagged1-activatedNotch1 signaling. *J Biol Chem* 280:15842-15848,2005
9. Liu T, Gao Y, Sakamoto K, Minamizato T, Furukawa K, Tsukazaki T, Shibata Y, Bessho K, Komori T, Yamaguchi A: BMP-2 promotes differentiation of osteoblasts and chondroblasts in Runx2-deficient cell lines. *J Cell Physiol* 211:728-735,2007
10. Minamizato T, Sakamoto K, Liu T, Kokubo H, Katsube K, Perbal B, Nakamura S, Yamaguchi A: CCN3/NOV inhibits BMP-2-induced osteoblast differentiation by interacting with BMP and Notch signaling pathways. *Biochem Bioph Res Co* 354:567-573,2007
11. Ishikuro M, Sakamoto K, Kayamori K, Izumo T, Yamaguchi A: Role of fibrous stroma in bone invasion by gingival squamous cell carcinomas. *BONE* 43:621-627,2008
12. Kayamori K, Sakamoto K, Nakashima T, Takayanagi T,

Morita K, Omura K, Nguyen ST, Miki Y, Iimura T, Himeno A, Akashi T, Yamada-Okabe H, Ogata E, Yamaguchi A: Roles of IL-6 and PTHrP in osteoclast formation associated with oral cancers: The significance of IL-6 synthesized by stromal cells in response to cancer cells. *Amer J Pathol* 176,968-980, 2010

13. Sakamoto K, Aragaki T, Kawachi H, Katsube K, Miki Y, Takizawa T, Omura K, Morita K, Okada N, Yamaguchi A: Down-regulation of keratin 4 and keratin 13 expression in oral squamous cell carcinoma and epithelial dysplasia: a clue for histopathogenesis. *Histopathol* 58:531-542,2011
14. Oue E, Lee JW, Sakamoto K, Iimura T, Aoki K, Kayamori K, Michi Y, Yamashiro M, Yamaguchi A: CXCL2 synthesized by oral squamous cell carcinoma is involved in cancer-associated bone destruction. *Biochem Bioph Res Co* 424:456-461,2012
15. Watanabe T, Tamamura Y, Hoshino A, Makino Y, Nishimura R, Kamioka H, Yoneda T, Amagasa T, Yamaguchi A, Iimura T: Increasing participation of Sclerostin in postnatal bone development revealed by three-dimensional immunofluorescence morphometry. *BONE* 51:447-458,2012
16. Sakamoto K, Fujii T, Kawachi H, Miki Y, Omura K, Morita K, Kayamori K, Khanom R, Katsube K, Yamaguchi A: Reduction of NOTCH1 expression pertains to maturation abnormalities of keratinocytes in squamous neoplasms. *Lab Invest* 92:688-702:2012
17. Matsushita Y, Sakamoto K, Tamamura Y, Shibata Y, Minamizato T, Kihara T, Ito M, Katsube K, Hiraoka S, Koseki H, Harada K, Yamaguchi A: CCN3 protein participates in bone regeneration as an inhibitory factor. *J Biol Chem* 288:19973-19985,2013
18. Sato K, Lee JW, Sakamoto K, Iimura T, Kayamori K, Yasuda H, Shindoh M, Ito M, Omura K, Yamaguchi A: RANKL synthesized by both stromal cells and cancer cells plays a crucial role in osteoclastic bone resorption induced by oral cancer. *Amer J Pathol* 182:1890-1899, 2013

MEMO

Forefront of osteoimmunology

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The bone marrow is one of the primary lymphoid organs that harbor the immune cells. Under these microenvironments, bone cells interact not only with other bone cells but also with immune cells including hematopoietic stem cells. Thus, all the cells in the bone marrow are communicating with each other to maintain both skeletal and immune systems [1,2]. However, the molecules that mediate the communication among cells in the bone have been poorly identified. We have tried to explore the molecular basis for cellular communication in the bone marrow and found that osteocyte-derived RANKL plays a crucial role in adult osteoclastogenesis [3], osteoclast-derived Sema4D inhibits bone formation [4] and osteoblast-derived Sema3A functions as a potent osteoprotective cytokine inhibiting osteoclastogenesis and promoting osteoblastogenesis [5]. As semaphorins, major axon guidance molecules, have emerged as bone cell communication factors, we are facing a new stage of bone research including the bone, immune and neural systems. We have long worked on the interaction between T cells and osteoclasts, and recently found the origin of osteoclastogenic Th17 cells to be Foxp3 positive Tregs [6]. The recent advances in osteoimmunology field including the conversion of Treg to pathogenic T cells will be discussed.

1. Takayanagi H. Nat Rev Immunol 7, 292-304 (2007),
2. Takayanagi H. Nat Rev Rheumatol 5(12), 667-76(2009),
3. Nakashima T. et al. Nat Med 17, 1231-34 (2011) ,
4. Negishi-Koga T. et al. Nat Med 17,1473-1480 (2011),
5. Hayashi M. et al. Nature 485, 69-74 (2012)
6. Komatsu N. et al. Nat Med, in press

CURRICULUM VITAE

Education

1990 M.D. The University of Tokyo, Tokyo, Japan
2001 Ph.D. (Medicine) The University of Tokyo, Tokyo, Japan

Award and Honors

2002 Amersham Biosciences and Science Prize for Young Scientists
2002 Novartis Japan Rheumatology Prize
2004 Japan College of Rheumatology Award
2004 Fuller Albright Award, ASBMR
2005 Japan Society for the Promotion of Science Prize
2005 Japan Academy Medal
2006 International Research Prize, Austrian Society for Bone and Mineral Research and Ludwig Boltzmann Institute of Osteology
2008 Academic Award of the Mochida Memorial Foundation
2009 Inoue Prize for Science
2009 JSBMR Distinguished Scientist Award
2011 IBMS-BONE Herbert A. Fleisch Award

Publications

1. Takayanagi H et al. *Nature* 408, 600-605 (2000)
2. Takayanagi H et al. *Nature* 416, 744-749 (2002)
3. Takayanagi H et al. *Dev Cell* 3, 889-901 (2002)
4. Koga T et al. *Nature* 428, 758-763 (2004)
5. Takayanagi H. *Nat Rev Immunol* 7, 292-304 (2007)
6. Asagiri M et al. *Science* 319, 624-627 (2008)
7. Shinohara M et al. *Cell* 132, 794-806 (2008)
8. Takayanagi, H *Nat Rev Rheumatol* 5(12), 667-76(2009)
9. Okamoto K et al. *Nature* 464, 1381-5 (2010)
10. Nakashima T et al. *Nat Med* 17, 1231-34 (2011)
11. Negishi-Koga, T., et al. *Nat Med* 17,1473-1480 (2011)
12. Hayashi, M., et al. *Nature* 485, 69-74 (2012)
13. Takayanagi H et al. *Cell Metab* 17(2):249-60.(2013)

MEMO

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Regenerative potential of the knee meniscus

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Osteoarthritis (OA) affects over 200 million people worldwide. Joints most frequently affected by OA are the hands, hips, spine and knees, where breakdown and subsequent loss of articular cartilage results in pain, stiffness and swelling and leads to decreased joint function and loss of joint mobility. The knee joint is particularly susceptible to OA and meniscal injuries are the most common knee injury. Treatment of meniscal injuries has evolved dramatically in the past 30 years in response to an increased understanding of the role performed by the meniscus within the knee joint, and today, surgical procedures are aimed at repairing or replacing damaged menisci, depending on the size of the injury and its location. Unfortunately, damaged meniscal tissue rarely regains the structural integrity and mechanical strength of normal meniscus, and recent data indicate that surgical repair of meniscal tears cannot reliably prevent the progression of degenerative changes and clinical symptoms that presage the development of knee OA. Particularly striking is the lack of options for reversing the progressive debilitation of the knee in young, healthy individuals.

Evidence from recent studies links the signaling pathways directing embryonic development with those that mediate adult tissue regeneration, where they influence the migration, proliferation and differentiation of locally residing tissue-specific stem/progenitor cells. In this way, the specificity of the reparative response generated by a tissue is dependent on the activation of the resident tissue-specific stem/progenitor cell population and not on the signals that affect their behavior. For adult musculoskeletal tissues, resident-specific stem/progenitor cells have been identified and characterized in muscle, tendon and ligament, articular cartilage and bone. As a group, these tissue-specific stem cells possess some of the characteristics of mesenchymal stem cells (MSC) but more importantly, exhibit characteristic tissue-specific identities. Based on the hypothesis that cells necessary for meniscal repair are those that express a characteristic gene signature that is defined during meniscal morphogenesis we combined laser-capture micro-dissection (LCM) of embryonic joint tissues with the production of tissue-specific libraries and comparative gene array analysis to uncover the gene signature of meniscus forming cells and the signaling pathways that regulate expression of these genes. Current efforts are aimed at using information gained from the study of meniscus development in mice to query the reparative potential of cells collected from adult mouse and human meniscus.

CURRICULUM VITAE

Education

1975 B.S., Biology, State University of New York at Stony Brook

1981 Ph.D., Cell Biology and Physiology, University of Connecticut

Position

1984-1988 Staff Scientist II, BMP Discovery Research, Genetics Institute

1986-1988 Principal Scientist, BMP Discovery Research, Genetics Institute

1988-1998 Senior Scientist, BMP Discovery Research, Genetics Institute

1998-2001 Director, Tissue Growth and Repair, Genetics Institute

2001 Distinguished Research Scientist, Genetics Institute/Wyeth Research

2001-2005 Senior Member of the Staff, The Forsyth Institute

2001-present Professor of Developmental Biology, Harvard School of Dental Medicine

2005-present Chair, Department of Developmental Biology, Harvard School of Dental Medicine

Award and Honors

2001 Honorary MA, Harvard University

2008 Kappa Delta Award, co-recipient, Orthopedic Research Society

2010 Marshall Urist Award in Tissue Repair, Orthopedic Research Society

2010 Basic Science Chair, 2010 ASBMR Meeting

2012 Harvard- Australia Foundation Fellowship

2012 Raine Medical Research Foundation Medal

Publications

1. Lanchoney TF, Olmstead EA, Shore EM, Gannon FA, Rosen V, Zasloff MA, and Kaplan FS. Characterization of bone morphogenetic protein 4 receptor in fibrodysplasia ossificans progressiva. *Clin Orthop Rel Res* 1998 ;346: 38-45.
2. Chen D, Ji X, Harris MA, Feng JQ, Karsenty G, Celeste AJ, Rosen V, Mundy GR, and Harris SE.. Differential roles for bone morphogenetic protein (BMP) receptor type IB and IA in differentiation and specification of mesenchymal precursor cells to osteoblast and adipocyte lineages. *J Cell Biol* 1998; 142: 295-305.
3. Furuya K, Nifuji A, Rosen V, and Noda M. Effects of GDF7/BMP12 on proliferation and alkaline phosphatase expression in rat osteoblastic osteosarcoma ROS 17/2.8 cells. *J Cell Biochem* 1999; 72: 177-180.
4. Lee M-H, Jaaved A, Kim H-J, Shin H-I, Gutierrez S, Choi J-Y, Rosen V, Stein JL, van Wijnen AJ, Stein GS, Lian JB, and Ryoo H-M. Transient upregulation of CBFA1 in response to bone morphogenetic protein-2 and transforming growth factor ß1 in C2C12 myogenic cells coincides with supression of the myogenic phenotype but is not sufficient for osteoblast differentiation. *J Cell Biochem* 1999; 73: 114-125.
5. Neuhaus H, Rosen V, and Thies RS. Heart specific expression of mouse BMP-10, a novel member of the TGF-ß superfamily. *Mech Dev* 1999; 80: 181-184.
6. Gamer LW, Wolfman NM, Celeste AJ, Hattersley G, Hewick R, and Rosen V. A novel BMP expressed in developing mouse limb, spinal cord, and tail bud is a potent mesoderm inducer in Xenopus embryos. *Dev Biol* 1999; 208: 222-232.
7. Valcourt U, Ronziere M-C, Winkler P, Rosen V, Herbage D, and Mallein-Gerin F. 1999. Different effects of bone morphogenetic proteins 2, 4, 12, and 13 on the expression of cartilage and bone markers in the MC615 chondrocyte cell line. *Exp Cell Res* 251: 264-274.
8. Ladher RHK, Church VL, Allen S, Robson L, Abdelfattah A, Brown NA, Hattersley G, Rosen V, Luyten FP, Dale L, and Francis-West PH. Cloning and expression of the Wnt antagonists Sfrp-2 and Frzb during chick development. *Dev Biol* 2000; 218: 183-198.
9. Weston AD, Rosen V, and Underhill TM. Regulation of skeletal progenitor differentiation by the BMP and retinoid signaling pathways. *J Cell Biol* 2000; 148: 679-690.
10. Yi SE, Daluiski A, Pederson R, Rosen V, Lyons KM. The type I BMPRIB is required for chondrogenesis in the mouse limb. *Development* 2000; 127(3):621-30.
11. Dailuski A, Engstrand T, Bahamonde M, Tompkinson K, Gamer LW, Rosen V, and Lyons KM. BMP3 is a negative regulator of bone density. *Nature Genet* 2001; 27: 84-88.
12. Gamer LW, Cox KA, Small C, and Rosen V. Gdf11 is a negative regulator of chondrogenesis and myogenesis in the developing chick limb. *Dev Biol* 2001; 229: 407-420.
13. Banerjee C, Javed A, Choi J-Y, Green J, Rosen V, van

Wijnen AJ, Stein JL, Lian JB, and Stein GS. Differential regulation of the two principal RunX/Cbfa1 N-terminal isoforms in response to BMP-2 during development of the osteoblast phenotype. *Endocrinol* 2001; 142: 4026-4039.

14. Schweitzer R, Chyung JH, Murtaugh LC, Brent AE, Rosen V, Olsen EN, Lassar A, and Tabin CJ. Analysis of the tendon cell fate using Scleraxis, a specific marker for tendons and ligaments. *Develop* 2001; 128: 3855-3886.
15. Thomopoulos S, Hattersley G, Rosen V, Mertens M, Galatz L, Williams GR, and Soslowsky LJ. The localized expression of extracellular matrix components in healing tendon insertion sites: an in situ hybridization study. *J Orthop Res* 2002; 20: 454-463.
16. Gamer, LW, Nove, J, and Rosen, V. Return of the Chalones. *Dev Cell* 2003; 4(3): 143-144.
17. Gamer, LW, Nove, J, Levin, M, and Rosen, V. BMP-3 is a novel inhibitor of BMP-4 and activin in Xenopus. *Dev Biol* 2005; 285: 156-168.
18. Chen H, Yong W, Ren S, Shen W, He Y, Cox KA, Zhu W, Li W, Soonpaa M, Payne RM, Franco D, Field LJ, Rosen V, Wang Y, and Shou W. Overexpression of BMP10 in myocardium disrupts cardiac postnatal hypertrophic growth. *J Biol Chem* 2006; 281: 27481-27491.
19. Bandyopadhyay A, Tsuji K, Harfe BD, Rosen V, and Tabin CJ. Genetic analysis of the roles of BMP2, BMP4 and BMP7 in limb patterning and skeletogenesis. *PLOS Genetics* 2006; 2: e216
20. Tsuji K, Bandyopadhyay A, Harfe BD, Cox KA, Kakar S, Gerstenfeld L, Einhorn T, Tabin CJ, and Rosen, V. BMP2 activity, although dispensable for bone formation, is required for the initiation of fracture healing. *Nat Genet*. 2006; 38: 1424-1429.
21. Tsuji K, Bandyopadhyay A, Harfe BD, Cox KA, Tabin CJ, and Rosen V. BMP4 is dispensable for skeletogenesis and fracture healing in the limb. *J Bone Joint Surg*. 2008; 90 (Suppl 1): 14-18.
22. Gamer LW, Ho V, Coc K, and Rosen V. Expression and function of BMP3 during chick limb development. *Dev Dyn* 2008; 237: 1691-1698.
23. Gamer LW, Cox K, Carlo JM, and Rosen V. Overexpression of BMP3 in the developing skeleton alters endochondral bone formation resulting in spontaneous rib fractures. *Dev Dyn*. 2009; 238: 2374-2381.
24. Alam N, St-Arnaud R, Lauzier D, Rosen V, and Hamdy RC. Are endogenous BMPs necessary for bone healing during distraction osteogenesis? *Clin Orthop Relat Res*. 2009; 467: 3190-3198.
25. Tsuji K, Cox K, Gamer L, Graf D, Economides A, and Rosen V. Conditional deletion of BMP7 from the limb skeleton does not affect bone formation or fracture repair. *J Orthop Res*. 2010; 28: 384-389.
26. Stankovic KM, Adachi O, Tsuji K, Kristiansen AG, Adams JC, Rosen V, and McKenna MJ. Differences in gene expression between the otic capsule and other bones. *Hear Res*, 2010; 265: 83-9. PMID: 20146935
27. Lowery JW, Pazin D, Intini G, Kobabu S, Chappius V, Capelo L and Rosen V. The role of BMP2 signaling in the skeleton. *Crit rev Eukaryot Gene Expr* 2011; 21: 177-185. PMID: 22077155
28. Lowery JW and Rosen V. Allele-specific RNA interference in FOPsilencing the FOP gene. *Gene Ther* 2012; 19: 701-2. PMID: 22130446
29. Gamer LW, Tsuji K, Cox K, Capelo LP, Lowery J, Beppu H, Rosen V. "BMPR-II is dispensable for formation of the limb skeleton" *Genesis*. 2011 Sep:49(9):719-24. PMID: 2153880
30. Kokabu S, Gamer L, Cox K, Lowery JW, Tsuji K, Economides A, Katagiri T, Rosen V. "BMP3 suppresses osteoblast differentiation of bone marrow stromal cells via interaction with Acvr2b." *J Mol Endocrinol*. 2012 Jan;26(1):87-94. PMID: 22074949
31. Chappuis V, Gamer L, Cox K, Lowery JW, Bosshardt DD and Rosen V. Periosteal BMP2 activity drives bone graft healing. *Bone* 2012; 51: 800-809. PMID: 22846673
32. Pazin, DE, Gamer LW, Cox KA, Rosen V. "Molecular profiling of synovial joints: use a microarray analysis to identify factors that direct the development of the knee and elbow." Dev Dyn 2012; 241 (11):1816-26. PMID: 22972626
33. Lowery JW, Lavigne AW, Kokabu S, and Rosen V. Comparative genomics identifies the mouse Bmp3 promoter and an upstream evolutionary conserved region (ECR) in mammals. PLoS One 2013; 8: e57840 PMID: 23451274
34. Whitman M, Rosen V, Brivanlou AH, Groppe JC, Sebald W and Mueller T. Regarding the mechanism of action of a proposed peptide agonist of the bone morphogenetic protein receptor activin-like kinase 3. *Nature Med* 2013; 19: 809-10. PMID: 23836213
35. Kokabu S, Nguyen T, Ohte S, Sato T, Katagiri T, Yoda T and Rosen V. TLE3, transducing-like enhancer of split 3, suppresses osteoblast differentiation of bone marrow stromal cells. *Biochem Biophys Res Commun* 2013; 438: 205-10.
36. Schminke B, Muhammad H, Bode C, Sadowski B, Gerter R, Gersdorff N, Burgers R, Monsonego-Ornan E, Rosen V, and Miosge N. A discoidin domain receptor 1 knock-out mouse as a novel model for osteoarthritis of the temporomandibular joint. *Cell Mol Life Sci* 2013; Aug 4 PMID: 23912900
37. Pazin DE, Gamer LW, Capelo LP, Cox KA and Rosen V. Gene signature of the embryonic meniscus. *J Orthop Res* 2013; Sept 21 PMID: 24108661
38. Wu X, Chim SM, Kuek V, Lim BS, Chow ST, Zhao J, Yang S, Rosen V, Tickner J and Xu J. HtrA1 is upregulated during RANKL-induced osteoclastogenesis, and negatively regulates osteoblast differentiation and BMP2-induced Smad1/5/8, ERK and p38 phosphorylation. *FEBS Letters*, in press.

MEMO

Combinatorial approach to identify gene regulation of inflammatory signals at RNA level

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miRNA is a member of ~ 22 nt non-cording RNA and play a critical role in the tissue or organ development and is also associated with human diseases. We recently found that miR-146 is highly expressed in rheumatoid arthritis synovium to regulate inflammation and that miR-140 is high in cartilage and important for tissue homeostasis against cartilage degradation.
Furthermore, now we are preparing series of genome wide analysis to examine the molecular mechanisms of inflammatory gene expression by non-coding RNA at the level of mRNA stability or translation.
Here, we introduce our recent results by next generation sequencing techniques, which revealed series of miRNAs involved in arthritis pathogenesis. To generate miRNA knockout mice in high-through put way, we applied TALEN system to delete miRNA gene in mice genome, which successfully leads us to analyze miRNA functions in vivo. We also show our strategy; cell based comprehensive gene screening to screen new molecules that regulates inflammatory gene expression. Combination of above methods may provide the novel aspect of RNA regulatory system and should promote our understanding of inflammatory diseases pathogenesis.

CURRICULUM VITAE

Education and Position

1992	Graduate from Okayama University, Japan
1992	Resident, Department of Orthopaedic Surgery, Okayama Saiseikai General Hospital, Japan
1994	Graduate Fellow, Department of Neuroscience, Institute of Molecular and Cellular medicine, Okayama University Medical School, Japan
1995	Graduate Fellow, Division of Rheumatology and Immunology, Institute of Medical Science, St.University School of Medicine, Japan
1997	Assistant Professor, Department of Orthopaedic Surgery, Okayama University Medical School, Japan
1997	Postdoctoral Research Fellow, Department of Cell Biology, Harvard Medical School, MA, USA
2000	Staff Scientist, Peptide Biology Laboratory, The Salk Institute for Biological Studies, CA, USA
2001	Scientist (Principal Investigator), JST, Precursory Research for Embryonic Science and Technology, Japan
2002	Assistant Professor, Department of Molecular and Experimental Medicine, The Scripps Research Institute, CA, USA
2004	Head, Department of Regenerative Biology and Medicine, National Research Institute for Child Health and Development, Japan
2010	Department Head, Department of Systems BioMedicine, National Research Institute for Child Health and Development, Japan
2011-pres.	Visiting Head, Department of Systems BioMedicine, National Research Institute for Child Health and Development, Japan
2011-pres.	Professor, Department of Systems BioMedicine, Graduate School and Faculty of Medicine, Tokyo Medical and Dental University, Japan

Publications

1. Nakasa T, Miyaki S, Okubo A, Hashimoto M, Nishida K, Ochi M, Asahara H. Expression of microRNA-146 in rheumatoid arthritis synovial tissue. *Arthritis Rheum*. 58(5): 1284-1292. (2008)
2. Nagata Y, Nakasa T, Mochizuki Y, Ishikawa M, Miyaki S, Shibuya H, Yamasaki K, Adachi N, Asahara H, Ochi M. Induction of apoptosis in the synovium of arthritic mice by intra-articular injection of double-stranded microRNA-15a. *Arthritis Rheum*. 60(9): 2677-2683. (2009)
3. Miyaki S, Nakasa T, Otsuki S, Grogan SP, Higashiyama R, Inoue A, Kato Y, Sato T, Lotz MK, Asahara H. MicroRNA-140 is expressed in differentiated human articular chondrocytes and modulates IL-1 responses. *Arthritis Rheum*. 60(9): 2723-2730. (2009)
4. Ito T, Yadav N, Lee J, Furumatsu T, Yamashita S, Yoshida K, Taniguchi N, Hashimoto M, Tsuchiya M, Ozaki T, Lotz M, Bedford MT, Asahara H. Arginine methyltransferase CARM1/PRMT4 regulates endochondral ossification. *BMC Dev Biol*. 9: 47. (2009)
5. Abe Y, Oka A, Mizuguchi M, Igarashi T, Ishikawa S, Aburatani H, Yokoyama S, Asahara H, Nagao K, Yamada M, Miyashita T. EYA4, deleted in a case with middle interhemispheric variant of holoprosencephaly, interacts with SIX3 both physically and functionally. *Hum Mutat*. 30(10): E946-955. (2009)
6. Kato Y, Miyaki S, Yokoyama S, Omori S, Inoue A, Horiuchi M, Asahara H. Real-time functional imaging for monitoring miR-133 during myogenic differentiation. *Int J Biochem Cell Biol*. 41(11): 2225-2231. (2009)
7. Kumagishi K, Nishida K, Yamaai T, Momota R, Miyaki S, Hirohata S, Naito I, Asahara H, Ninomiya Y, Ohtsuka A. A disintegrin and metalloproteinase with thrombospondin motifs 9 (ADAMTS9) expression by chondrocytes during endochondral ossification. *Arch Histol Cytol*. 72(3): 175-185. (2009)
8. Yokoyama S, Ito Y, Ueno-Kudoh H, Shimizu H, Uchibe K, Albini S, Mitsuoka K, Miyaki S, Kiso M, Nagai A, Hikata T, Osada T, Fukuda N, Yamashita S, Harada D, Mezzano V, Kasai M, Puri PL, Hayashizaki Y, Okado H, Hashimoto M, Asahara H. A systems approach reveals that the myogenesis genome network is regulated by the transcriptional repressor RP58. *Dev Cell*. 17(6): 836-848. (2009)
9. Ito Y, Toriuchi N, Yoshitaka T, Ueno-Kudoh H, Sato T, Yokoyama S, Nishida K, Akimoto T, Takahashi M, Miyaki S, Asahara H. The Mohawk homeobox gene is a critical regulator of ten don differentiation. *Proc Natl Acad Sci U S A*. 107(23): 10538-10542. (2010)
10. Otsuki S, Grogan SP, Miyaki S, Kinoshita M, Asahara H, Lotz MK. Tissue neogenesis and STRO-1 expression in immature and mature articular cartilage. *J Orthop Res*. 28(1): 96-102. (2010)
11. Higashiyama R, Miyaki S, Yamashita S, Yoshitaka T,

Lindman G, Ito Y, Sasho T, Takahashi K, Lotz M, Asahara H. Correlation between MMP-13 and HDAC7 expression in human knee osteoarthritis. *Mod Rheumatol*. 20(1): 11-17. (2010)

12. MizutaniR, Nakamura K, Yokoyama S, Sanbe A, Kusakawa S, Miyamoto Y, Torii T, Asahara H, Okado H, Yamauchi J, Tanoue A. Developmental expression of sorting nexin 3 in the mouse central nervous system. *Gene Expr Patterns*. 11(1-2):33-40. (2010)
13. Miyaki S, Sato T, Inoue A, Otsuki S, Ito Y, Yokoyama S, Kato Y, Takemoto F, Nakasa T, Yamashita S, Takada S, Lotz MK, Ueno-Kudo H, Asahara H. MicroRNA-140 plays dual roles both in cartilage development and homeostasis. *Genes Dev*. 24(11): 1173-1185. (2010)
14. Otsuki S, Hanson SR, Miyaki S, Grogan SP, Kinoshita M, Asahara H, Wong CH, Lotz MK. Extracellular sulfatases support cartilage homeostasis by regulation BMP and FGF signaling pathways. *Proc Natl Acad Sci U S A*. 107(22): 10202-10207. (2010)
15. Asada M, Rauch A, Shimizu H, Maruyama H, Miyaki S, Shibamori M, Kawasome H, Ishiyama H, Tuckermann J, Asahara H. DNA binding-dependent glucocorticoid receptor activity promotes adipogenesis via Krüppel-like factor 15 gene expression. *Lab Invest*. 91(2):203-15. (2011)
16. Awazawa M, Ueki K, Inabe K, Yamauchi T, Kubota N, Kaneko K, Kobayashi M, Iwane A, Sasako T, Okazaki Y, Ohsugi M, Takamoto I, Yamashita S, Asahara H, Akira S, Kasuga M, Kadowaki T. Adiponectin Enhances Insulin Sensitivity by Increasing Hepatic IRS-2 Expression via a Macrophage-Derived IL-6-Dependent Pathway. *Cell Metab*. 13(4):401-12. (2011)
17. Wada S, Kato Y, Okutsu M, Miyaki S, Suzuki K, Yan Z, Schiaffino S, Asahara H, Ushida T, Akimoto T. Translational suppression of atrophic regulators by microRNA-23a integrates resistance to skeletal muscle atrophy. *J Biol Chem*. 286(44):38456-65. (2011)
18. Miyaki S, Asahara H. Macro view of microRNA function in osteoarthritis. *Nature Rev Rheumatol*. 8(9):543-52. (2012) (Review)
19. Fukami M, Tsuchiya T, Takada S, Kanbara A, Asahara H, Igarashi A, Kamiyama Y, Nishimura G, Ogata T. Complex genomic rearrangement in the SOX9 5' region in a patient with Pierre Robin sequence and hypoplastic left scapula. *Am J Med Genet A*. 158A(7):1529-34. (2012)
20. Yamashita S, Miyaki S, Kato Y, Yokoyama S, Sato T, Barrionuevo F, Akiyama H, Scherer G, Takada S, Asahara H. L-Sox5 and Sox6 proteins enhance chondrogenic miR-140 microRNA expression by strengthening dimeric Sox9 activity. *J Biol Chem* 287 (26), 22206-22215 (2012)
21. Uchibe K, Shimizu H, Yokoyama S, Kuboki T, Asahara H. Identification of novel transcription-regulating genes expressed during murine molar development. *Dev Dyn*. 241(7):1217-26. (2012)
22. Furumatsu T, Asahara H. Chromatin assembly and in vitro transcription analyses for evaluation of individual protein activities in multicomponent transcriptional complexes. *Methods Mol Biol*. 977:193-202. (2013) (Review)
23. Gibson G, Asahara H. microRNAs and cartilage. *J Orthop Res*. Sep;31(9):1333-44. (2013) (Review)
24. Watanabe T, Oyama T, Asada M, Harada D, Ito Y, InagawaM, Suzuki Y, Sugano S, Katsube K, Karsenty G, Komori T, Kitagawa M, Asahara H. MAML1 enhances the transcriptional activity of Runx2 and plays a role in bone development. *PLOS Genetics*. 9(1):e1003132. (2013)
25. Matsukawa T, Sakai T, Yonezawa T, Hiraiwa H, Hamada T, Nakashima M, Ono Y, Ishizuka S, Nakahara H, Lotz MK, Asahara H, Ishiguro N. MicroRNA-125b regulates the expression of aggrecanase-1 (ADAMTS-4) in human osteoarthritic chondrocytes. *Arthritis Res Ther*. 15(1):R28. (2013)
26. Hasegawa A, Nakahara H, Kinoshita M, Asahara H, Koziol J, Lotz MK. Cellular and extracellular matrix changes in anterior cruciate ligaments during human knee aging and osteoarthritis. *Arthritis Res Ther*. 15(1):R29 (2013)
27. Rakoczy J, Fernandez-Valverde SL, Glazov EA, Wainwright EN, Sato T, Takada S, Combes AN, Korbie DJ, Miller D, Grimmond SM, Little MH, Asahara H, Mattick JS, Taft RJ, Wilhelm D. MicroRNAs-140-5p/140-3p modulate Leydig cell numbers in the developing mouse testis. *Biol Reprod*. 88(6):143. (2013)
28. Nakahara H, Hasegawa A, Otabe K, Ayabe F, Matsukawa T, Onizuka N, Ito Y, Ozaki T, Lotz MK, Asahara H. Transcription factor mohawk and the pathogenesis of human anterior cruciate ligament degradation. *Arthritis Rheum*. 65(8):2081-9. (2013)
29. Yoshitaka T, Kawai A, Miyaki S, Numoto K, Kikuta K, Ozaki T, Lotz M, Asahara H. Analysis of microRNAs expressions in chondrosarcoma. *J Orthop Res*. in press
30. Shimizu H, Kubo A, Uchibe K, Hashimoto M, Yokoyama S, Takada S, Mitsuoka K, Asahara H, The AERO System: a 3D-like Approach for Recording Gene Expression Patterns in the Whole Mouse Embryo, *PLOS One*. in press
31. Takada S, Sato T, Ito Y, Yamashita S, Kato T, Kawasumi M, Kanai-Azuma M, Igarashi A, Kato T, Tamano M, AsaharaH. Targeted gene deletion of miRNAs in mice by TALEN system, *PLOS One*. in press
32. Onizuka N, Ito Y, Inagawa M, Nakahara H, Takada S, Lotz MK, Toyama Y, Asahara H. The Mohawk homeobox transcription factor regulates the differentiation of tendons and volar plates. *J Orthop Science*. in press
33. Kato T, Miyata K, Sonobe M, Yamashita S, Tamano M, Miura K, Kanai Y, Miyamoto S, Sakuma T, Yamamoto T, Inui M, Kikusui T, Asahara H*, and Takada S*. Production of Sry knockout mouse using TALEN via oocyte injection. *Scientific Rep*. in press (* equally contributed corresponding authors)

MEMO

Craniofacial dysmorphogenesis and infantile hemangioma – the antrax toxin receptor connection

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Infantile hemangiomas are the most common tumors of infancy. Typically, they appear within a few days/weeks after birth and grow rapidly during a few months (proliferative phase). After about a year they start to involute (involution phase) and after a period of several months/years, they are replaced by fibro-fatty tissue. Hemangiomas are more common in females than in males and they occur most frequently in the head and neck region of affected infants. Our studies have demonstrated that the rapid proliferation of infantile hemangiomas is caused by defects in the regulation of vascular endothelial growth factor receptor 1 (VEGFR1) in endothelial cells of the tumor. When normal endothelial cells are stimulated by VEGF or activated by binding to extracellular matrix, expression of the VEGF decoy receptor VEGFR1 is stimulated and VEGFR2-dependent signaling constrained. In contrast, hemangioma endothelial cells in their proliferative phase exhibit constitutive low levels of VEGFR1 expression and high levels of VEGF-dependent VEGFR2 signal transduction. This is a consequence of defects that result in local loss of function of a cell surface integrin-like receptor known as Anthrax toxin receptor 1 (ANTXR1)/Tumor endothelial marker 8 (TEM8) in hemangioma endothelial cells. Mice that are homozygous for Tem8 null alleles have changes in dermal blood vessels that are similar to those seen in hemangioma tumors. In addition, the mice exhibit growth retardation, bone loss and craniofacial defects similar to those seen in patients with the recessive GAPO syndrome. Patients with this syndrome are homozygous for loss-of-function mutations in TEM8 and exhibit growth retardation, alopecia, pseudo-anodontia and optic atrophy, as well as other craniofacial defects, bone loss and hemangioma. TEM8 is therefore a critical regulator of vascular endothelial and osteoblastic functions in addition to controlling the activities of growth plates and synchondroses at the skull base.

References:

1. Jinnin, M., et al., *Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma*. Nat. Med., 2008. 14(11): p. 1236-1246.

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2000 Honorary Doctor of Science Degree, University of Medicine and Dentistry of New Jersey
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2001 Distinguished Faculty Award, Harvard School of Dental Medicine
2006 H.C. Jacobæus Prize and lecturer, H.C. Jacobæus' Forelæsninger Foundation, Sweden
2006 Member, ScanBalt Academy
2006 Senior Research Prize, American Society of Matrix Biology
2007 Co-chairman, Gordon Research Conference "Cartilage Biology & Pathology"
2009 Chairman, Gordon Research Conference "Cartilage Biology & Pathology"
2009 Co-chairman, Gordon Research Conference "Bones and Teeth"
2010 IADR Distinguished Scientist Award for Craniofacial Biology Research
2010 ISMB Distinguished Investigator Award
2010 American Association for the Advancement of Science Fellow
2011 Henry Gray Award, American Association of Anatomists
2011 Chairman, Gordon Research Conference "Bones and Teeth"
2011 Fellow, American Association of Anatomists
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Publications

1. Sun, X-D, Jeng, L, Bolliet, C, Olsen, BR, Spector, M. Non-viral endostatin plasmid transfection of mesenchymal stem cells via collagen scaffolds. *Biomaterials*, 2009 30:1222-1231.
2. Hou, B, Kolpakova-Hart, E, Fukai, N, Wu, K, Olsen, BR. The polycystic kidney disease 1 (Pkd1) gene is required for the responses of osteochondroprogenitor cells to midpalatal suture expansion in mice. *Bone*, 2009, 44:1121-1133. PMC2680722
3. Faye, C, Chautard, E, Olsen, BR, Ricard-Blum, S. The first draft of the endostatin interaction network. J. Biol. Chem. 2009, 284:22041-22047. PMC2755928
4. Galli, C, Fu, Q, Wang, WF, Olsen, BR, Manolagas, SC, Jilka, R, and O' Brien, CA. Commitment to the osteoblast lineage is not required for RANKL gene expression. J Biol Chem 2009, 284:12654-12662. PMC2675994
5. Olsen, BR. Genetics of human skeletal disease. In: *The Skeletal System*, ed. Olivier Pourquié. Cold Spring Harbor Laboratory Press. 2009, pp. 317-340.
6. Boye, E, Jinnin, M, Olsen, BR. Infantile hemangioma – challenges, new insights and therapeutic promise. *J Craniof Surg*, 2009, 20:1-7. PMID: 19190505.
7. Boye, E, Olsen, BR. Signaling mechanisms in infantile hemangioma. *Curr Opin Hematol*. 2009, 16:202–208. PMC2895461
8. Xu, L, Polur I, Lim C, Servais JM, Dobeck J, Li Y, Olsen BR. Early-onset osteoarthritis of mouse temporomandibular joint induced by partial discectomy. Osteoarthr Cartilage 2009, 17:917-922. PMC2941347
9. Gebauer, JM, Keene, DR, Olsen, BR, Sorokin, LM, Paulsson, M, Wagener, R. Mouse AMACO, a kidney and skin basement membrane associated molecule that mediates RGD-dependent cell attachment. *Matrix Biol* 2009, 28:456-462. (No BRO grant)
10. Olsen BR. When primary cilia fail. *Matrix Biol* 2009; 28: 443-4. Review. PMID: 19939339.
11. Mukherjee, PM, Wang, CJ, Chen, I-P, Jafarov, T, Olsen, BR, Yueki, Y, Reichenberger, EJ. Cherubism gene Sh3bp2 is important for optimal bone formation, osteoblast differentiation and function. Am J Orthod Dentofacial Orthop. 2010, 138:140.e1-140.e11. PMC3268358
12. Besschetnova, TY, Kolpakova-Hart, E, Guan, Y, Zhou, J, Olsen, BR, Shah, JV. Identification of signaling pathways regulating primary cilium length and flow-mediated adaptation. Curr. Biol., 2010, 20:182-187. PMC2990526.
13. Harnagea, C, Vallie`res, M, Pfeffer, CP, Wu, D, Olsen, BR, Pignolet, A, Legare, F, Gruverman, A.Two-dimensional nanoscale structural and functional imaging in individual collagen type-I fibrils. *Biophys J*, 2010, 98: 3070-3077. PMC2884257
14. Nicolae, C, Olsen, BR. Unexpected matrix diseases and novel therapeutic strategies. Cell Tissue Res. 2010, 339:155–165. Review
15. Jinnin, M, Ishihara, T, Boye, E, Olsen, BR. Recent progress

in studies of infantile hemangioma. *J Derm*. 2010, 37:283-298. Review.

16. Faye, C, Inforzato, A, Bignon, M, Hartmann, DJ, Muller, L, Ballut, L Olsen, BR, Day, AJ, Ricard-Blum, S. Transglutaminase-2: a new endostatin partner in the extracellular matrix of endothelial cells. *Biochem. J*. 2010, 427:467-475. PMCID: PMC2876729.
17. Jeng, L, Olsen, BR, Spector, M. Engineering endostatin-producing cartilaginous constructs for cartilage repair using non-viral transfection of chondrocyte- and mesenchymal stem cell (msc)-seeded collagen scaffolds. *Tiss Eng Part A*, 2010, 16:3011- 3021. PMC3189205
18. Clarkin, C, Olsen, BR. On bone-forming cells and blood vessels in bone development. Preview. *Cell Metabol*, 2010, 12:314-316. Preview. PMC3031181
19. Medici, D, Shore, EM, Lounev, VY, Kaplan, FS, Kalluri, R, Olsen, BR. Conversion of vascular endothelial cells into multipotent stem-like cells. *Nat Med* 2010, 16: 1400-1406. PMC3209716
20. Mauney, J, Olsen, BR, Volloch V. Matrix remodeling as stem cell recruitment event: a novel in vitro model for homing of human bone marrow stromal cells to the site of injury shows crucial role of extracellular collagen matrix. *Matrix Biol*. 2010, 29:657-663.
21. Medici, D, Olsen, BR. Transforming blood vessels into bone. *Cell Cycle* 2011, 10:362-363. Free full text http://www.landesbioscience.com/journals/cc/article/14519/
22. Pfeffer CP, Olsen BR, Ganikhanov F, Legare F. Imaging skeletal muscle using harmonic generation and coherent anti-Stokes Raman scattering microscopy. *Biomed Opt Express* 2011; 27: 1366-76. PMC3087593
23. Berendsen A, Olsen BR. Tankyrase loses its grip on SH3BP2 in cherubism. *Cell* 2011; 147: 1222-3. PMID: 22153068.
24. Jeng, L, Olsen, BR, Spector, M. Engineering endostatin-expressing cartilaginous constructs using injectable biopolymer hydrogels. *Acta Biomat*, 2012, 8:2203-2212. PMID: 22370447 (no NIH grant).
25. Ionescu, I, Kozhemyakina, E, Nicolae, C, Kaestner, KH, Olsen, BR, Lassar, AB. FoxA family members are crucial regulators of the hypertrophic chondrocyte differentiation program. *Dev Cell* 2012; 22: 927-39. PMC3356573
26. Papadaki, ME, Lietman, SA, Levine, MA, Olsen, BR, Kaban LB, Reichenberger, EJ. Cherubism: Best clinical Practice. . *Orphanet J Rare Dis*. 2012, 7 Suppl 1:S6. PMC3359956
27. Reichenberger, EJ, Levine, MA, Olsen, BR, Papadaki, ME, Lietman, SA. The role of SH3BP2 in the pathophysiology of cherubism. *Orphanet J Rare Dis*. 2012, 7 Suppl 1:S5. PMC3359958
28. Jumlongras, D, Lachke, SA, O'Connell, DJ, Aboukhalil, A, Li, X, Choe, SE, Ho, JW, Turbe-Doan, A, Robertson, EA, Olsen, BR, Bulyk, ML, Amendt, BA, and Maas, RL. An Evolutionarily Conserved Enhancer Regulates Bmp4 Expression in Developing Incisor and Limb Bud. *PLoS ONE* 2012; 7: e38568. PMC3373496
29. Medici, D, Olsen, BR. The role of endothelial-mesenchymal transition in heterotopic ossification. *JBMR* 2012; 27: 1619-22. PMID: 22806925. Review.
30. Katebi N, Kolpakova-Hart E, Lin CY, Olsen BR. The mouse palate and its cellular responses to midpalatal suture expansion forces. *Ortho Craniofac Res* 2012; 15: 148-158. NIHMS512089
31. Medici, D. and Olsen, B.R. (2012). Transformation of Vascular Endothelial Cells into Multipotent Stem-Like Cells: Role of the Activin-Like Kinase-2 Receptor. Stem Cells and Cancer Stem Cells: Therapeutic Applications in Disease and Injury. Springer. Volume 8, Chapter 19
32. Medici, D, Olsen, BR. Rapamycin inhibits proliferation of hemangioma endothelial cells by reducing HIF-1-dependent expression of VEGF. *PLoS ONE*, 2012;7(8):e42913. PMC3416768
33. Liu, Y, Berendsen, A, Jia, S, Lotinun, S, Baron, R, Ferrara, N, Olsen, BR. Intracellular VEGF regulates the balance between osteoblast and adipocyte differentiation. *JCI*, 2012; 122:3101-3112. PMC3428080
34. Adams, A, McBratney-Owen, B, Newby, B, Bowen, M, Olsen, BR, Warman, ML. Presphenoidal synchondrosis fusion in DBA/2J mice. *Mammal Genome*, 2013, 24:54-62. PMC3560942
35. Olsen, BR. Matrix molecules and their ligands. In: Principles of Tissue Engineering. R.G. (Lanza, R, Langer, R, and Vacanti, J. ed). 4nd ed., in press, Academic Press, pp.
36. Duncan, MD, Yang, C, Tanjore, H, Boyle, PM, Keskin, D, Sugimoto, H, Zeisberg, M, Olsen, BR, Kalluri, R. Type XVIII collagen is essential for survival during acute liver injury. *Dis Model Mech*, 2013 Apr 4. Epub ahead of print. Free full text.
37. Toh, WS, Foldager, CB, Olsen, BR, Spector, M. Basement membrane molecule expression attendant to chondrogenesis by nucleus pulposus cells and mesenchymal stem cells. *J Orthop Res*, 2013, Epub ahead of print. (no NIH grant)
38. Volloch, V, Olsen, BR. Why cellular stress suppresses adipogenesis in skeletal tissue, but is ineffective in adipose tissue: Control of mesenchymal cell differentiation via integrin binding sites in extracellular matrices. Mat Biol, 2013 Jun 18. doi:pii: S0945-053X(13)00091-7. 10.1016/j.matbio.2013.06.001. [Epub ahead of print]. NIHMSID #504634
39. Berendsen, AD, Olsen, BR. Osteoblast-adipocyte lineage plasticity in tissue development, maintenance and pathology. Review. Cell Mol Life Sci. in press. NIHMS514666
40. Olsen, BR, Ehrlich, YH, Yalak. Extracellular protein phosphorylation revisited. Submitted for publication. Opinion.
41. Liu, Y, Olsen, BR. Distinct VEGF functions during bone development and homeostasis. Submitted for publication.
42. Berendsen, AD, Olsen, BR. How Vascular Endothelial Growth Factor A (VEGF) Regulates Differentiation of Mesenchymal Stem Cells. JHC, Submitted for publication. Review. NIH Bone grant support.

MEMO

Cartilage and meniscus regeneration with synovial stem cells

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According to our previous studies, the number of mesenchymal stem cells (MSCs) in synovial fluid increase in knees with anterior cruciate ligament injury (Rheumatology 2008), meniscus injury (Clin Orthop Relat Res 2014), and osteoarthritis (J Orthop Res 2011). The morphology and gene profiles in synovial fluid MSCs were more similar to those in synovial MSCs than in bone marrow MSCs. Principal component analysis of gene profiles for various mesenchymal tissues-derived MSCs and chondrocytes demonstrated that MSCs from intraarticular tissues and chondrocytes were closer to each other than MSCs from extraarticular tissues (J Orthop Res 2008). Synovium may be a reservoir for MSCs to contribute to the intraarticular tissue repair. After intraarticular tissues, such as cartilage, meniscus, and ligament, are injured, MSCs may be mobilized from synovium to synovial fluid, adhere to the injured site, and contribute to the repair. However, the number of MSCs is limited, therefore, the injured tissues cannot be healed in the natural course. Transplantation of enough number of synovial MSCs to the injured tissues may promote intraarticular tissue healing.

MSCs are attractive cell source for cartilage and meniscus regeneration. Our *in vitro* and *in vivo* chondrogenic assay demonstrated that synovial and bone marrow MSCs had a higher chondrogenic ability than adipose and muscle MSCs (Arthritis Rheum 2005, Cell Tissue Res 2007, Cell Tissue Res 2008). Human synovial MSCs expanded more in human serum than bone marrow MSCs (Arthritis Rheum 2008). In rat, rabbit, and pig studies, transplantation of synovial MSCs promoted cartilage and meniscus regeneration (Stem Cells 2007, Stem Cells 2009, Cytotherapy 2012, Osteoarthritis Cartilage 2012, J Bone Joint Surg Am 2012, Biochem Biophys Res Commun 2013).

Current cell therapy for cartilage and meniscus regeneration requires invasive procedures. We have developed a novel implantation procedure with synovial MSCs. Cartilage or meniscus defect is filled with synovial MSC suspension for 10 minutes. According to our *in vitro* and *in vivo* studies, more than 60% cells adhered to the defect, and promoted cartilage and meniscus regeneration (Arthritis Res Ther 2008, J Orthop Res 2013).

We are currently doing clinical trial for cartilage regeneration. All patients have their cartilage defects filled with synovial MSCs arthroscopically. Favorable results are obtained by MRI imaging in many cases, by second look arthroscopies, and by biopsies. Our method has such advantages that no periosteal coverage or scaffold were required and that transplantation is possible arthroscopically. We are also trying to regenerate osteoarthritis of the knee with osteotomy or meniscus centralization (Arthrosc Tech 2012) by using synovial MSCs. We are going to start another clinical trial for meniscus treatment with synovial MSCs.

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Publications

1. Transplantation of neuronal cells induced from human mesenchymal stem cells improves neurological functions after stroke without cell fusion. Xu H, Miki K, Ishibashi S, Inoue J, Sun L, Endo S, Sekiya I, Muneta T, Inazawa J, Dezawa M, Mizusawa H.
   J Neurosci Res. 2010;88(16):3598-609.
2. Repair of olecranon fractures using fiberWire without metallic implants: report of two cases. Nimura A, Nakagawa T, Wakabayashi Y, Sekiya I, Okawa A, Muneta T. J Orthop Surg Res. 2010 Oct 12;5:73.
3. Effect of CT slice thickness on accuracy of implant positioning in navigated total hip arthroplasty. Hirasawa N, Matsubara M, Ishii K, Hagio S, Okuda N, Sekiya I, Muneta T. Comput Aided Surg. 2010 Nov 2.
4. Intradiscal transplantation of synovial mesenchymal stem cells prevents intervertebral disc degeneration through suppression of matrix metalloproteinase-related genes in nucleus pulposus cells in rabbits. Miyamoto T, Muneta T, Tabuchi T, Matsumoto K, Saito H, Tsuji K, Sekiya I. Arthritis Res Ther. 2010;12(6):R206.
5. Hip acetabular dysplasia and joint laxity of female anterior cruciate ligament-injured patients. Yamazaki J, Muneta T, Ju YJ, Morito T, Okuwaki T, Sekiya I. Am J Sports Med. 2011 Feb;39(2):410-4.
6. Radiographic description of femoral tunnel placement expressed as intercondylar clock time in double-bundle anterior cruciate ligament reconstruction. Yamazaki J, Muneta T, Koga H, Sekiya I, Ju YJ, Morito T, Yagishita K. Knee Surg Sports Traumatol Arthrosc. 2011 Mar;19(3):418-23.
7. Ketoprofen absorption by muscle and tendon after topical or oral administration in patients undergoing anterior cruciate ligament reconstruction. Sekiya I, Morito T, Hara K, Yamazaki J, Ju YJ, Yagishita K, Mochizuki T, Tsuji K, Muneta T. AAPS PharmSciTech. 2010 Mar;11(1):154-8.
8. BMP-7 inhibits cartilage degeneration through suppression of inflammation in rat zymosan-induced arthritis. Takahashi T, Muneta T, Tsuji K, Sekiya I. Cell Tissue Res. 2011 May;344(2):321-32.
9. High-flex Posterior Cruciate-Retaining vs Posterior Cruciate-Substituting Designs in Simultaneous Bilateral Total Knee Arthroplasty A Prospective, Randomized Study. Yagishita K, Muneta T, Ju YJ, Morito T, Yamazaki J, Sekiya I. J Arthroplasty. 2012 Mar;27(3):368-74.
10. Effects of different initial bundle tensioning strategies on the outcome of double-bundle ACL reconstruction: a cohort study. Muneta T, Koga H, Ju YJ, Yagishita K, Sekiya I. Sports Med Arthrosc Rehabil Ther Technol. 2011 Jul 28;3:15.
11. Surgical management of grade 3 medial knee injuries combined with cruciate ligament injuries. Koga H, Muneta T, Yagishita K, Ju YJ, Sekiya I. Knee Surg Sports Traumatol Arthrosc. 2012 Jan;20(1):88-94.
12. Human mesenchymal stem cells in synovial fluid increase in the knee with degenerated cartilage and osteoarthritis.

Sekiya I, Ojima M, Suzuki S, Yamaga M, Horie M, Koga H, Tsuji K, Miyaguchi K, Ogishima S, Tanaka H, Muneta T. J Orthop Res. 2012 Jun;30(6):943-9.
13. The Effect of Graft Fixation Angles on Anteroposterior and Rotational Knee Laxity in Double-Bundle Anterior Cruciate Ligament Reconstruction: Evaluation Using Computerized Navigation. Koga H, Muneta T, Yagishita K, Ju YJ, Sekiya I. Am J Sports Med. 2012 Mar;40(3):615-23. Epub 2011 Nov 22.
14. Arthroscopic, histological and MRI analyses of cartilage repair after a minimally invasive method of transplantation of allogeneic synovial mesenchymal stromal cells into cartilage defects in pigs. Nakamura T, Sekiya I, Muneta T, Hatsushika D, Horie M, Tsuji K, Kawarasaki T, Watanabe A, Hishikawa S, Fujimoto Y, Tanaka H, Kobayashi E. Cytotherapy. 2012 Mar;14(3):327-38.
15. Implantation of allogenic synovial stem cells promotes meniscal regeneration in a rabbit meniscal defect model. Horie M, Driscoll MD, Sampson HW, Sekiya I, Caroom CT, Prockop DJ, Thomas DB. J Bone Joint Surg Am. 2012 Apr 18;94(8):701-12.
16. Hyaluronan injection therapy for athletic patients with patellar tendinopathy. Muneta T, Koga H, Ju YJ, Mochizuki T, Sekiya I. J Orthop Sci. 2012 Apr 17.
17. Remnant volume of anterior cruciate ligament correlates preoperative patients' status and postoperative outcome. Muneta T, Koga H, Ju YJ, Horie M, Nakamura T, Sekiya I. Knee Surg Sports Traumatol Arthrosc. 2012 Apr 28.
18. Intra-articular injection of human mesenchymal stem cells (MSCs) promote rat meniscal regeneration by being activated to express Indian hedgehog that enhances expression of type II collagen. Horie M, Choi H, Lee RH, Reger RL, Ylostalo J, Muneta T, Sekiya I, Prockop DJ. Osteoarthritis Cartilage. 2012 Oct;20(10):1197-207.
19. Isolation and characterization of multipotential mesenchymal cells from the mouse synovium Futami I, Ishijima M, Kaneko H, Tsuji K, Ichikawa-Tomikawa N, Sadatsuki R, Muneta T, Arikawa-Hirasawa E, Sekiya I, Kaneko K. PLoS One. 2012;7(9):e45517.
20. Incidence and risk factors for medial tibial stress syndrome and tibial stress fracture in high school runners. Yagi S, Muneta T, Sekiya I. Knee Surg Sports Traumatol Arthrosc. 2012 Aug 9.
21. Osteopontin level in synovial fluid is associated with the severity of joint pain and cartilage degradation after anterior cruciate ligament rupture Yamaga M, Tsuji K, Miyatake K, Yamada J, Abula K, Ju YJ, Sekiya I, Muneta T. PLoS One. 2012;7(11):e49014
22. Properties and usefulness of aggregates of synovial mesenchymal stem cells as a source for cartilage regeneration. Suzuki S, Muneta T, Tsuji K, Ichinose S, Makino H, Umezawa A, Sekiya I. Arthritis Res Ther. 2012 Jun 7;14(3):R136.
23. Arthroscopic centralization of an extruded lateral meniscus. Koga H, Muneta T, Yagishita K, Watanabe T, Mochizuki T, Horie M, Nakamura T, Okawa A, Sekiya I. Arthrosc Tech. 2012 Oct 22;1(2):e209-12.
24. Intraoperative Joint Gaps Affect Postoperative Range of Motion in TKAs With Posterior-stabilized Prostheses. Watanabe T, Muneta T, Sekiya I, Banks SA. Clin Orthop Relat Res. 2013 Apr;471(4):1326-33.
25. Human YKL39 (chitinase 3-like protein 2), an osteoarthritis-associated gene, enhances proliferation and type II collagen expression in ATDC5 cells. Miyatake K, Tsuji K, Yamaga M, Yamada J, Matsukura Y, Abula K, Sekiya I, Muneta T. Biochem Biophys Res Commun. 2013 Feb 1;431(1):52-7.
26. Comparative sequential morphological analyses during in vitro chondrogenesis and osteogenesis of mesenchymal stem cells embedded in collagen gels. Ichinose S, Tagami M, Muneta T, Mukohyama H, Sekiya I. Med Mol Morphol. 2013 Mar;46(1):24-33.
27. The kinematic analysis of female subjects after double-bundle anterior cruciate ligament reconstruction during single-leg squatting. Yamazaki J, Muneta T, Ju YJ, Koga H, Morito T, Sekiya I. J Orthop Sci. 2013 Mar;18(2):284-9.
28. Effect of Posterolateral Bundle Graft Fixation Angles on Graft Tension Curves and Load Sharing in Double-Bundle Anterior Cruciate Ligament Reconstruction Using a Transtibial Drilling Technique. Koga H, Muneta T, Yagishita K, Ju YJ, Mochizuki T, Horie M, Nakamura T, Okawa A, Sekiya I. Arthroscopy. 2013 Mar;29(3):529-38.
29. Isolation and characterization of human mesenchymal stem cells derived from shoulder tissues involved in rotator cuff tears. Utsunomiya H, Uchida S, Sekiya I, Sakai A, Moridera K, Nakamura T. Am J Sports Med. 2013 Mar;41(3):657-68.
30. Synovial stem cells in musculoskeletal regeneration. Atesok K, Doral MN, Bilge O, Sekiya I. J Am Acad Orthop Surg. 2013 Apr;21(4):258-9. 5.
31. Intraarticular Injection of Synovial Stem Cells Promotes Meniscal Regeneration in a Rabbit Massive Meniscal Defect Model. Hatsushika D, Muneta T, Horie M, Koga H, Tsuji K, Sekiya I. J Orthop Res. 2013 Sep;31(9):1354-9.
32. Transplantation of aggregates of synovial mesenchymal stem cells regenerates meniscus more effectively in a rat massive meniscal defect. Katagiri H, Muneta T, Tsuji K, Horie M, Koga H, Ozeki N, Kobayashi E, Sekiya I. Biochem Biophys Res Commun. 2013 Jun 14;435(4):603-9.
33. Effect of femoral tunnel position on graft tension curves and knee stability in anatomic double-bundle anterior cruciate ligament reconstruction. Koga H, Muneta T, Yagishita K, Watanabe T, Mochizuki T, Horie M, Nakamura T, Sekiya I. Knee Surg Sports Traumatol Arthrosc. 2013 Sep 24.
34. Transplantation of Achilles tendon treated with BMP-7 promotes meniscus regeneration in a rat massive meniscus defect model. Ozeki N, Muneta T, Koga H, Katagiri H, Otabe K, Okuno M, Tsuji K, Kobayashi E, Matsumoto K, Saito H, Saito T, Sekiya I. Arthritis Rheum. 2013 Jul 29.

MEMO

Fracture repair and beta-catenin in aging and disease : implications for an approach to therapy

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The pace of fracture repair slows with aging, but the critical mediators in this process are now known. Here we determined the relative contribution of mesenchymal progenitor cell age, hematopoietic cell age, and circulating factors on *in vivo* bone regeneration and *in vitro* osteoblast differentiation. Exposure to youthful circulation by heterochronic parabiosis reversed the slowed fracture repair characteristic of aging in mice. This rejuvenation resulted in increased mineralization and osteoblastic activity of old mesenchymal progenitor cells. To determine if circulating cells played a role in this rejuvenation, we examined the ability of old and young bone marrow cells in which we could delete cells with osteogenic potential to enhance the osteogenic capacity of old bone marrow cells. Conditioned media from an adherent population of young cells rejuvenated the osteogeneic capacity of old cells. Similarly, engraftment of young hematopoietic cells into old animals rescued fracture repair and osteogenic potential in a mechanism that did not require osteoblasts from the donor animal. β-catenin signaling, a pathway important in bone regeneration and osteoblast differentiation, was shown to be modulated during rejuvenation. Reduction of β-catenin signaling during early fracture repair improved bone regeneration in old mice. These data demonstrate that the circulatory system carries within it a "youth factor" that is able to rejuvenate bone repair and osteoblast differentiation through modulation of β-catenin. This data raises the possibility that agents that modulate β-catenin can improve the quality of bone repair in the aging population.

CURRICULUM VITAE

Education

High School Northeast High school, Philadelphia, Pennsylvania USA 1978 High School Diploma

College University of Pennsylvania, Philadelphia, Pennsylvania, USA 1982. BSc, Material Science and Engineering (Summa cum Laude)

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Position

2002 - present University of Toronto, Toronto, Ontario, Canada, Member, Collaborative Program in Developmental Biology

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2002 - present The Research Institute of the Hospital for Sick Children, Toronto, Ontario, Canada, Senior Scientist, Program in Developmental and Stem Cell Biology

2004 - present University of Toronto, Toronto, Ontario, Canada, Vice Chair Research, Surgery

2004 - present University of Toronto, Toronto, Ontario, Canada, Professor, Surgery

2004 - present University of Toronto, Toronto, Ontario, Canada, Professor, Laboratory Medicine and Pathobiology

2005 - present The Hospital for Sick Children, Toronto, Ontario, Canada, Head, Division of Orthopaedics

2006 – present University of Toronto, Toronto, Ontario, Canada, A.J. Latner Professor and Chair of Orthopaedics

2011 - present University of Toronto, Toronto, Ontario, Canada, Interim Director, Toronto Musculoskeletal Centre (Extra-Departmental Unit)

Award and Honors

2013 2013 ASE Award for Excellence in Innovation, Association for Surgical Education, Los Angles, California, United States. (Distinction) Awarded to the Toronto Orthopaedic Boot Camp. Annual award for exemplary performance in surgical education with the intent to recognize novel ideas and/or methods for improving teaching and learning.

2012 Fellowship in the Canadian Academy of Health Sciences, Canadian Academy of Health Sciences, Ottawa, Ontario, Canada. Fellows of the Academy are elected on the basis of their demonstrated leadership, creativity, distinctive competencies and commitment to advance academic health sciences.

Publications

1. Chen Y, Alman BA. Wnt pathway, an essential role in bone regeneration. Journal of Cellular Biochemistry. 2009: 106(3): 353-362.
2. Gurung A, Uddin F, Hill RP, Ferguson PC, Alman BA. Beta-catenin is a mediator of the response of the fibroblasts to irradiation. American Journal of Pathology. 2009: 174(1): 248-255.
3. Giampietro PF, Dunwoodie SL, Kusumi K, Pourquie O, Tassy O, Offiah AC, Cornier AS, Alman BA, Blank RD, Raggio CL, Glurich L, Turnpenny PD. Progress in the understanding of the genetic etiology of vertebral segmentation disorders in humans. Annals NY Academy of Science. 2009: 1151: 38-67.
4. Lavoie JF, Biernaskie JA, Chen Y, Bagli D, Alman B, Kaplan DR, Miller FD. Skin-derived precursors differentiate into skeletogenic cell types and contribute to bone repair. Stem Cells Development. 2009: 18(6): 893-906.
5. Ho L, Alman B. Protecting the hedgerow: p53 and hedgehog pathway. Cell Cycle. 2010: 9(3): 506-511.
6. Lipa JE, Qiu W, Huang N, Alman BA, Pang CY. Pathogenesis of radiation-induced capsular contracture in tissue expander and implant breast reconstruction. Plastic Reconstruction Surgery. 2010: 125(2): 437-445.
7. Szauter KM, Ordas A, Laxer RM, Pope E, Wherrett D, Alman B, Mink M, Boyd CD, Csiszar K, Hinek A. A novel fibrotic disorder associated with increased dermal fibroblast proliferation and downregulation of genes of the microfibrillar network. British Journal of Dermatology. 2010: 163(5): 1102-1115.
8. Offiah A, Alman B, Corneir AS, Giampietro PF, Tassy O, Wade A, Turnpenny PD, ICVAS (International Consortium for Vertebral Anomalies and Scoliosis). Pilot assessment of a radiologic classification system for segmentation defects of the vertebrae. American Journal of Medical Genetics Part A. 2010: 152A(6): 1357-1371.
9. Bovée JVMG, Hogendoorn PC, Wunder JS, Alman BA. Cartilage tumors and bone development: Molecular pathology and hints into therapeutic targets. Nature Reviews Cancer. 2010: 10(7): 481-488.
10. Alman BA, Wedge J. Robert Bruce Salter, C.C., MD, FRCSC. Dec 15, 1924 - May 10, 2010. Journal of Children's Orthopaedics. 2010: 4(4): 275-276.
11. Amini-Nik S, Kraemer D, Cowan ML, Gunaratne K, Nadesan P, Alman BA, Miller JD. Ultrafast mid-IR laser scalpel: Protein signals of the fundamental limits to minimally invasive surgery. PLoS ONE. 2010: 5(9): pii: e13053.
12. Wu C, Amini Nik S, Nadesan P, Stanford WL, Alman BA. Aggressive fibromatosis (desmoid tumor) is derived from mesenchymal progenitor cells. Cancer Research. 2010: 70(19): 7690-7698.
13. Rockel JS, Alman BA. Don't hedge your bets: Hedgehog signaling as a central mediator of enchondral bone

development and cartilage diseases. Journal of Orthopaedic Research. 2011: 29(6): 810-815.
14. Sonnadara RR, Van Vliet A, Safir O, Alman B, Ferguson P, Kraemer W, Reznick R. Orthopaedic Bootcamp: Examining the effectiveness of an intensive surgical skills course. Surgery. 2011: 149(6): 745-749.
15. Hong H, Nadesan P, Poon R, Alman BA. Testosterone regulates cell proliferation in aggressive fibromatosis (desmoid tumour). British Journal of Cancer. 2011: 104(9): 1452-1458.
16. Bielefeld KA, Amini-Nik S, Whetstone H, Poon R, Youn A, Wang J, Alman BA. Fibronectin and beta-catenin act in a regulatory loop in dermal fibroblasts to modulate cutaneous healing. Journal of Biological Chemistry. 2011: 286(31): 27687-27697.
17. Hsu SC, Zhang X, Yu C, Li ZJ, Wunder JS, Hui CC, Alman BA. Kif7 promotes Hedgehog signaling in growth plate chondrocytes by restricting the inhibitory function of Sufu. Development. 2011: 138(17): 3791-3801.
18. Amini-Nik S, Glancy D, Boimer C, Whetstone H, Keller C, Alman BA. Pax7 expressing cells contribute to dermal wound repair tegulating scar size through a beta-catenin mediated process. Stem Cells. 2011: 29(9): 1371-1379.
19. Robanus-Maandag E, Bosch C, Amini-Nik S, Knijnenburg J, Szuhai K, Cervera P, Poon R, Eccles D, Radice P, Giovannini M, Alman BA, Tejpar S, Devilee P, Fodde R. Familial adenomatous polyposis-associated desmoids display significantly more genetic changes than sporadic desmoids. PLoS ONE. 2011: 6(9): e24354.
20. Atesok KI, Alman BA, Schemitsch EH, Peyser A, Mankin H. Osteoid osteoma and osteoblastoma. Journal of the American Academy of Orthopaedic Surgeons. 2011: 19(11): 678-689.
21. Alman BA, Kelley SP, Nam D. Heal thyself: Using endogenous regeneration to repair bone. Tissue Engineering. Part B Rev. 2011: 17(6): 431-436.
22. Fattah A, Cypel T, Donner EJ, Wang F, Alman BA, Zuker RM. The first successful lower extremity transplantation: 6-year follow-up and implications for cortical plasticity. American Journal of Transplant. 2011: 11(12): 2762-2767.
23. Wang CY, Wei Q, Han I, Sato S, Ghanbari-Azarnier R, Whetstone H, Poon R, Hu J, Zheng F, Zhang P, Wang W, Wunder JS, Alman BA. Hedgehog and notch signaling regulate self-renewal of undifferentiated pleomorphic sarcoma. Cancer Research. 2012: 72(4): 1013-1022.
24. Zolkipli Z, Sherlock M, Biggar WD, Taylor G, Hutchison JS, Peliowski A, Alman BA, Ling SC, Tein I. Abnormal fatty acid metabolism in spinal muscular atrophy may predispose to perioperative risks. European Journal of Pediatric Neurology. 2012: 16(5): 549-553.
25. Sparrow DB, Chapman G, Smith AJ, Mattar MZ, Major JA, O'Reilly VC, Saga Y, Zackai EH, Dormans JP, Alman BA, McGregor L, Kageyama R, Kusumi K, Dunwoodie SL. A mechanism for gene-environment interaction in the etiology of congenital scoliosis. Cell. 2012: 149(2): 295-306.
26. Poon R, Hong H, Wei X, Pan J, Alman BA. A high throughput screen identifies Nefopam as targeting cell proliferation in β-catenin driven neoplastic and reactive fibroproliferative disorders. PLoS ONE. 2012: 7(5): e37940.
27. McAdam LC, Mayo AL, Alman BA, Biggar WD. The Canadian experience with long-term deflazacort treatment in Duchenne muscular dystrophy. Acta Myol. 2012: 31(1): 16-20.
28. Sonnadara RR, Garbedian S, Safir O, Nousiainen M, Alman B, Ferguson P, Kraemer W, Reznick R. Orthopaedic Boot Camp II: Examining the retention rates of an intensive surgical skills course. Surgery. 2012: 151(6): 803-807.
29. Nam D, Mau E, Wang Y, Wright D, Silkstone D, Whetstone H, Whyne C, Alman B. T-lymphocytes enable osteoblast maturation via IL-17F during the early phase of fracture repair. PLoS ONE. 2012: 7(6): e40044.
30. Ali SA, Alman B. RNA extraction from human articular cartilage by chondrocyte isolation. Analytical Biochemistry. 2012:429 (1): 39-41.
31. Black KP, Alman BA, Levine WN, Nestler SP, Pinney SJ. Orthopaedic Resident Education - It's a whole new game: "If I'm going to be a spine surgeon, why do I need to learn how to reconstruct an anterior cruciate ligament?" AOA critical issues. Journal of Bone and Joint Surgery (Am). 2012: 94(13).
32. Maezawa Y, Binnie M, Li C, Thorner P, Hui C-C, Alman B, Taketo MM, Quaggin SE. A new Cre driver mouse line, Tcf21/Pod1-Cre, targets metanephric mesenchyme. PLoS ONE. 2012: 7(7): e40547.
33. Tsoi KM, Dai Q, Alman BA, Chan WC. Are quantum dots toxic? Exploring the discrepancy between cell culture and animal studies. Acc Chem Res. 2012: Aug 1 (Epub ahead of print).
34. Bielefeld KA, Amini-Nik S, Alman BA. Cutaneous wound healing: Recruiting developmental pathways for regeneration. Cellular and Molecular Life Sciences. 2012: Oct 4 (Epub ahead of print).
35. Hsu C, Zhang X, Cheng S, Wunder JS, Hui CC, Alman BA. Suppressor of fused (Sufu) mediates the effect of Parathyroid hormone-like hormone (Pthlh) on chondrocyte differentiation in the growth plate. Journal of Biological Chemistry. 2012: 287(43): 36222-36228.
36. Ho L, Ali SA, Al-Jazrawe M, Kandel R, Wunder JS, Alman BA. Primary cilia attenuate Hedgehog signalling in neoplastic chondrocytes. Oncogene. 2012: Dec 17 (Epub ahead of print)..
37. Camp M, Mattingly DA, Gross AE, Nousiainen MT, Alman BA, McKneally MF. Patients' vies on surgeons' financial conflicts of interest. Journal of Bone and Joint Surgery (Am). 2013: 95(2): e91-98.
38. Alman BA, Ferguson P, Kraemer W, Nousiainen MT, Reznick RK. Competency-based education: a new model for teaching orthopaedics. Instr Course Lect. 2013;62:565-9.

MEMO

Osteoclast as MDSC (myeloid-derived suppressor cell) and its role in ONJ and tumor bone metastasis

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Current therapeutic strategies of catabolic bone diseases such as osteoporosis and metastatic tumors in bone target osteoclasts in order to reduce or normalize the elevated bone resorption activity. Both bisphosphonates and humanized monoclonal antibody against RANKL are such anti-resorptive agents achieving this therapeutic goal albeit through different pharmacokinetics.

Osteonecrosis of the jaw (ONJ) in maxilla and mandible has emerged, however, as a rare but severe side effect reported between 0.5% to 18% among those patients who were treated with anti-resoptive agents. While clinical presentations vary significantly, ONJ symptoms commonly demonstrate the lack of resolution in chronic inflammation of oral mucosa. Oral mucosa is composed of stratified epithelium and thin connective tissue, and considered one of the most protective tissue barriers from environmental stresses, chemical damage and bacterial infection. Barrier tissues are known to contain T cells expressing a canonical gammadelta T cell receptor. Immunosurveillance and prompt response to injury by the barrier tissue are thought to involve gammadelta T cells.

Our recent studies using Tcrd-H2BEGFP mice demonstrated the prolonged retention of gammadelta T cells in gingival/palatal tissue after maxillary molar extraction when mice were injected with zoledronate (ZOL). Furthermore, the development of ONJ-like lesion was significantly modulated in ZOL-treated Tcrd-/- mice. Thus, we postulate that the close approximation between jawbone and oral barrier immunity may, in part, contribute to the pathogenesis of ONJ.

It was noted that animal models of ONJ-like lesion revealed an unusual co-localization of inflammatory cells with ZOL-affected osteoclasts. Osteoclasts are differentiated from the monocytic lineage of myeloid immune cells with the presence of M-CSF and RANKL. Once differentiated, osteoclasts have been considered to function as bone cells. However, the unique and consistent observation on the distinct association between ZOL-affected osteoclasts and lymphocytes as well as neutrophils may suggest a yet uncovered function of osteoclasts as immune cells.

Our preliminary characterization of osteoclasts derived from human CD14+ monocytes suggested the secretion of a set of cytokines. Typically, osteoclastic cytokines exhibited a similar profile of myeloid-derived suppressor cells (MDSC). MDSC not only suppresses lymphocytes contributing to the resolution of inflammation; but further supports tissue repair by inducing vascular formation and secreting growth factors. This presentation will highlight a new concept of osteoclast activities as an immune cells, in particular, with MDSC-like characteristics. Contributions of osteoclasts to physiological bone remodeling and coupling with osteoblasts, as well as pathological contributions to ONJ and metastatic tumors in bone marrow will be discussed.

CURRICULUM VITAE

Education

1981 D.D.S. Tokyo Dental College, Tokyo, Japan
1986 D.M.Sc. Harvard University, Cambridge, MA (Ph.D. equivalent)
1986 Certificate Postgraduate Prosthodontics (Board Eligible) Harvard School of Dental Medicine, Boston, MA
1993 D.M.D. Harvard School of Dental Medicine, Boston, MA

Position

1990-93 Faculty Member, Committee of Cell & Developmental Biology Harvard Medical School, Boston, MA
1994-97 Associate Professor of Prosthetic Dentistry Harvard School of Dental Medicine, Boston, MA
1997-99 Associate Professor (with tenure) Advanced Prosthodontics, Biomaterials and Hospital Dentistry UCLA School of Dentistry, Los Angeles, CA
1999-Present Professor (with tenure) Advanced Prosthodontics, Biomaterials and Hospital Dentistry UCLA School of Dentistry, Los Angeles, CA
2000-Present Professor of Oral Biology (Joint Appointment) UCLA School of Dentistry, Los Angeles, CA
2012-Present Affiliate Professor of Bioengineering Department of Bioengineering UCLA Henry Samueli School of Engineering and Applied Science

Award and Honors

2000 Fellow of Biotechnology: Policy Issues and Regulatory Frameworks Salzburg Seminar, Salzburg, Austria
2000 Appreciation of Service U.S. Department of Health and Human Services, Public Health Service, NIH, National Institute of Dental Craniofacial Research
2004 Distinguished Scientist Award in Prosthodontics and Implantology International Association for Dental Research
2004 Theodore M. Hesburgh Certificate of Excellence for Faculty Development to Enhance Undergraduate Teaching and Learning UCLA Freshman Cluster Program Faculty member in Biotechnology and Society TIAA-CREF
2005 Appreciation of Service U.S. Department of Health and Human Services, Public Health Service, NIH, National Institute of Dental Craniofacial Research

Publications

1. Yuki I、Lee D, Murayama Y, Chiang A, Vinters HV, Nishimura I, Wang JCC, Ishii A, Benjamin WM, Vinuela F: Thrombosis and healing in the experimental aneurysm model, part II: Thrombus organization in the setting of bioabsorbable polymers, *J Neurosurg*, 107:109-120, 2007.
2. Nishimura I: Nanotechnology and its applications in dental implant, *Clin Res Dent*, 4:29-35, 2007.
3. Thakor D, Spigelman I, Tabata Y, Nishimura I.: Subcutaneous peripheral injection of cationized gelatin/ DNA polyplexes as a platform for noninvasive gene transfer to sensory neurons, *Molecular Therapy*, 15:2124-2131, 2007.
4. Egusa H, Iida K, Kobayashi M, Lin T, Zhu M, Zuk P, Hedrik M, Nishimura I: Down-regulation of extracellular matrix-related gene cluster during osteogenic differentiation of bone marrow and adipose tissue-derived stromal cells. *Tissue Eng*, 13:2589-2600, 2007.
5. Oh J, Wang CJ, Poole M, Kim E, Davis RC, Nishimura I, Pae EK: The genome segment on mouse chromosome 12 determines maxilla, *J Dent Res*, 86:1203-1206, 2007.
6. Wang CJ, Iida K, Egusa H, Hokugo A, Jewett A, Nishimura I: Trabecular bone deterioration in *col9a1+/-* mice associated with enlarged osteoclasts adhered to collagen IX-deficient bone, *J Bone Miner Res*, 23(6):837-849, 2008.
7. Oh J-H, Nishimura I.: Copy number variation in the human genome and its implication for human disease. *J Korean Acad Maxillofac Plastic Reconstruc Surg*, 30:205-212, 2008.
8. Thakor DK, Lin A, Matsuka Y, Meyer E, Ruangsri S, Nishimura I, Spigelman I: Increased peripheral nerve excitability and local NaV1.8 mRNA up-regulation in painful neuropathy, *Mol Pain*, 5(1):14, 2009. [Open access] [*Highly accessed article*]
9. Kelly J, Lin A, Wang CJ, Park S, Nishimura I: The effect of vitamin D insufficiency on implant osseointegration. *J Prosthodont*, 18(6):473-478, 2009.
10. Lin A, Wang CJ, Kelly J, Gubbi P, Nishimura I: The role of titanium implant surface modification with hydroxyapatitite nanoparticles in progressive early bone-implant fixation *in vivo*. *Int J Oral Maxiofac Implants*, 24(5):808-816, 2009.
11. Nishimura I, Thakor D, Lin A, Ruangsri S, Spigelman I: Molecular strategies for therapeutic targeting of primary sensory neurons in chronic pain syndromes, In *Translational Pain Research: From Mouse to Man*, Ed. Kruger L, Light A. pp139-161, CRC Press, Boca Raton, FL, 2009.
12. Lin A, Hokugo A, Choi J, Nishimura I: Small coiled-coil cytoskeleton-associated molecule, FGFR1OP2/wit3.0 facilitates fibroblast-driven wound closure. *Am J Pathol*, 176(1):108-121, 2010.
13. Hokugo A, Christensen R, Chung EM, Sung EC, Felsenfeld AL, Sayer J, Garrett N, Adams JS, Nishimura I: Increased prevalence of bisphosphonate-related osteonecrosis of the jaw with vitamin D deficiency in rats. *J Bone Min Res*,

25(6):1337-49, 2010.
14. Nishimura, I: Implant interface to bone tissue: Biomimetic surface functionalization through nanotechnology, In *Interface Oral Health Science 2009*, Ed, Fukumoto T, Iwamori M, Suzuki O, pp60-66, Springer Japan, Tokyo, Japan, 2010.
15. Yuki I, Uchiyama N, Murayama Y, Nien YL, Lee D, Ebara M, Ishii A, Chiang A, Vinters HV, Nishimura I, Wu BM, Vinuela F: Intravascular tissue reactions induced by various types of bioabsorbable polymeric materials: correlation between the degradation profiles and corresponding tissue reactions. *Neuroradiology*, 52(11):1017-24, 2010.
16. Lin A, Hokugo A, Nishimura I: Wound closure and wound management: A new therapeutic molecular target. *Cell Adhesion & Migration*, 4(3):396-399, 2010.
17. Mussano F, Lee K, Zuk P, Tran L, Cacalano N, Jewett A, Carossa S, Nishimura I: Differential effect of ionizing radiation exposure on multipotent and differentiation-restricted bone marrow mesenchymal stem cells. *J Cell Biochem*, 111(2):322-32, 2010.
18. Nishimura I.: GEM21S: Future perspectives of dental biologics (commissioned review: in Japanese). *Dental Diamond*, 2010.
19. Cohen M, Nishimura I, Tamplen M, Hokugo A, Beumer J, Steinberg M, Shu JD, Abemayer E, Nabili V: Animal model of radiogenic bone damage to study mandibular osteoradionecrosis, *Am J Otolaryngol*, 32(4):291-300, 2011.
20. Mengatto CM, Mussano F, Honda Y, Colwell C, Nishimura I: Circadian rhythm and cartilage extracellular matrix genes in osseointegration: A genome-wide screening of implant failure by vitamin D deficiency. *PloS One*, 6(1):e15848, 2011.
21. Suwanwela J, Lee J, Lin A, Ucer C, Devlin H, Sinsheimer J, Garrett N, Nishimura I: A Genetic Association Study of Single Nucleotide Polymorphisms in FGFR1OP2/wit3.0 and Long-term Atrophy of Edentulous Mandible. *PloS One*, 6(1):e16204, 2011.
22. Templeton M, Trapp K, Nishimura I, Armin B, Steinberg M, Beumer J, Abemayor E, Nabili V: Standardized analysis of mandibular osteoradionecrosis in a rat model, *Otolaryngol Head Neck Surg*, 145(3):404-10, 2011.
23. Butz F, Ogawa T, Nishimura I: Interfacial shear strength of endosseous implants, *Int J Oral Maxillofac Imp*, 26(4):746-51, 2011.
24. Mawardi H, Giro G, Kajiya M, Ohta K, Almazrooa S, Alshwaimi E, Woo S-B, Nishimura I, Kawai T: A role of oral bacteria in bisphosphonate-induced osteonecrosis of jaw, *J Dent Res*, 90(11):1339-45, 2011.
25. Ruangsri S, Lin A, Mulpuri Y, Lee K, Spigelman I, Nishimura I: Axonal Nav1.8 mRNA accumulation and sciatic nerve injury-induced painful neuropathy in rats, *J Biol Chem*, 286(46):39836-47, 2011.
26. Honda Y, Ding X, Mussano F, Wiberg A, Ho CM, Nishimura I: Application of feedback system control (FSC) to identify the optimized osteogenic drug cocktails, *IEEE*, 10.1109/MHS.2011.6102147, 2011.
27. Armin BB, Hokugo A, Nishimura I, Tamplen M, Beumer JIII, Steinberg ML, Abemayor E, Nabili V. Brachytherapy-mediated bone damage in a rat model investigating maxillary osteoradionecrosis, *Arch Otolaryngol Head Neck Surg*, 138(2):167-171, 2012.
28. Kahenasa N, Sung E, Nabili V, Kelly J, Garret N, Nishimura I: Resolution of pain and complete healing of mandibular osteoradionecrosis using pentoxifylline and tocopherol, a case report, *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol*, 113(4):e18-e23, 2012.
29. Cheng W, Nishimura I: High Throughput Screening of Biologically Functional Small Molecules for Modulating the Expression of FGFR1OP2/wit3.0 in Fibroblasts, *J Cal Dent Assoc*, 40(12):929-31, 934-7, 2012.
30. Hokugo A, Sun S, Park S, McKenna C, Nishimura I: Equilibrium-dependent bisphosphonate interaction with crystalline bone mineral explains the anti-resorptive pharmacokinetics and the prevalence of osteonecrosis of the jaw in a rat model, *Bone*, 53(1):59-68, 2013.
31. Ha J, Osher SJ, Nishimura I: Mathematical filtering minimized metallic halation of titanium implant in microCT image, *J Cal Dent Assoc*, 41(1):41-5, 2013.
32. Devlin H, Nishimura I (Editors): Oral and Cranial Implants – Recent Research Development, Springer, Heidelberg, Germany, 2013.
33. Nishimura I: Genetic background of implant failure, in *Oral and Cranial Implants – Recent Research Developments*, Devlin H, Nishimura I, Eds. Springer, Heidelberg, Germany, 2013.
34. Park S, Nishimura I: Biosphosphonates and dental implant treatment, in *Oral and Cranial Implants – Recent Research Developments*, Devlin H, Nishimura I, Eds. Springer, Heidelberg, Germany, 2013.
35. Nishimura I: Genetic networks in osseointegration, *J Dent Res*, in press, 2013.
36. Honda Y, Ding X, Mussano F, Wiberg A, Ho CM, Nishimura I: Guiding osteogenic fate of mouse and human mesenchymal stem cells through feedback system control, *Scientific Reports*, Accepted, 2013.
37. Kelly JA, Mallya S, Nabili V, Nishimura I: Current clinical management of intraoral osteoradionecrosis, *J Prosthet Dent*, Submitted, 2013.
38. Nishimura I: Acquisition and maintenance of osseointegration, *In Implant Surgery*, Beumer JIII Ed. Quintessence, Chicago, IL, Submitted, 2013.
39. Nishimura I, Garrett N, Beumer J: Edentulous patients, Patterns of bone resorption and clinical outcomes: osseointegrated implants, *In Implant Surgery*, Beumer JIII Ed. Quintessence, Chicago, IL, Submitted, 2013.

MEMO

Poster Session

Retreat 2014

Poster Session List

Name	Grade
Ma Chengshan	4
Nurmaa Dashzeveg	4
Bijaya Haobam	4
Rumana Khanom	4
Duarte Puerto Carolina Lizeth	4
Zayar Lin	4
Junpei Shirakawa	4
Yukihiko Hashida	4
Md.Sofiqul Islam	4
Mayumi Ogita	4
Nadila Wali	4
Tadashi Hosoya	4
Naoki Kimura	4
Warunee Pluemsakunthai	4
Cheng Xu	4
Gerardo Jose Joves Mendez	4
Masayoshi Uezono	4
Dawud Abduweli	3
Gu Jie	3
Suphanantachat Supreda	3
Li Hui	3
Surapornsawasd Thunyaporn	3
Thanit Prasitsak	3
Rajapakshe Mudiyanselage Anupama Rasadari Rajapakshe	3
Thanatvarakorn Ornnicha	3
Yusuke Matsuo	3
Yoko Yoshihashi	3
Maheswari Kuppusamy	3
Mohannad Issa Michael Nassar	3
Kenji Ogura	3
Kahaer Abula	3
Takayuki Yamada	3
Uehara Daniela Tiaki	2
Nuylan, Michelle Loyola	2
Alaa Abdulahad Turkistani	2
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Name	Grade
Hua Qiao	2
Khunkar, Sahar Jameel M	2
Kenchi Takenaka	2
Kong Kalyan	2
Baba Bista	2
Makiri Kawasaki	2
Natsuka Umezawa	1
Jun Yamada	4
Takashi Taniyama	4
Munetaka　Iwata	4
Arata Yuki	4
Madoka Onuma	4
Nobutake Ozeki	4
Yu Matsukura	3
Yusuke Nakagawa	3
Hidetoshi Kaburagi	2
Masanori Saito	2
Satoshi Sumiya	2
Katsuaki Yanagisawa	2
Makiko Inoue	2
Mio Udo	2
Shinpei Kondo	2
Ryusuke Saito	2
Toshiyuki Ohara	2
Mikio Shioda	1
Kaori Nakamura	1
Hiroaki Yasuda	1
Jinying Piao	
Koji Fujita	

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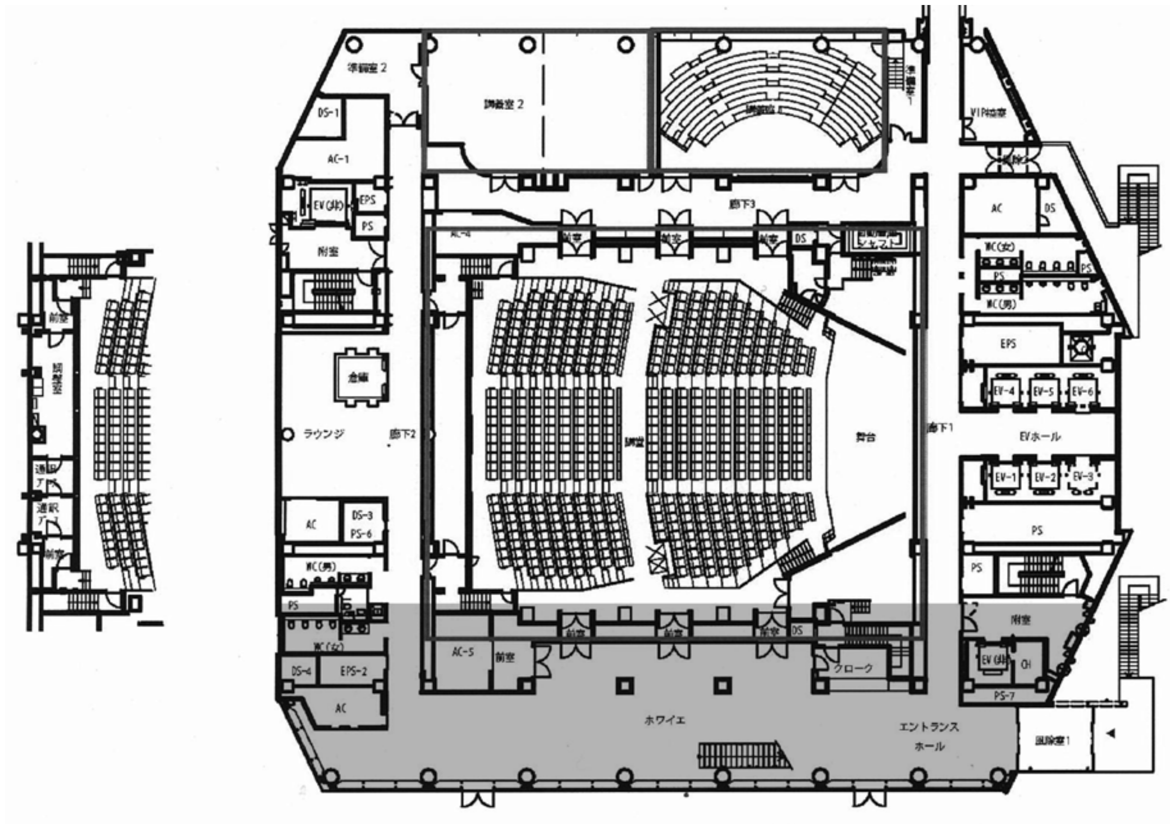
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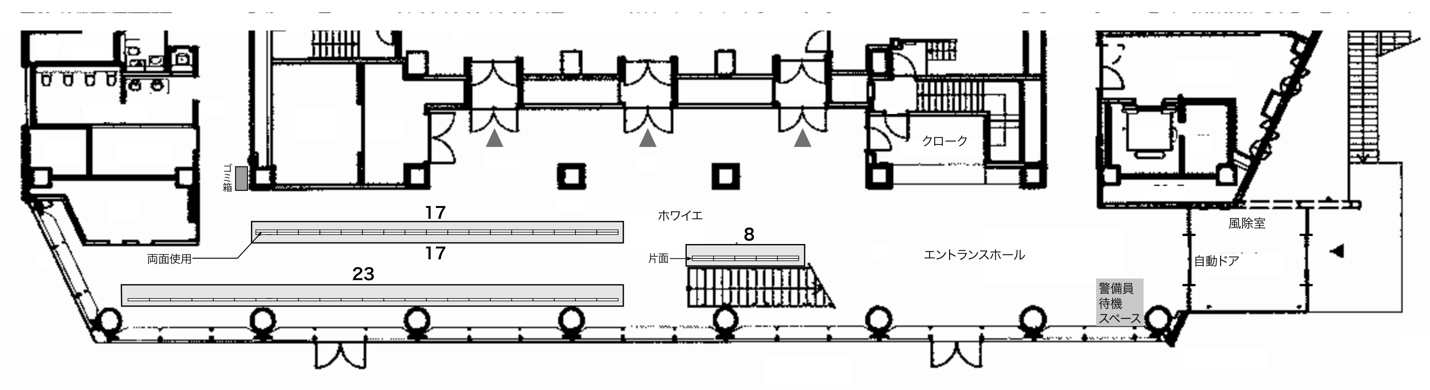
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