UNIVERSITY OF OXFORD WORKSHOP

Advances in the Molecular Pharmacology and Therapeutics of Bone Disease

10-12 JULY 2007

and

NATIONAL ASSOCIATION FOR THE RELIEF OF PAGET'S DISEASE

International Symposium on Paget's Disease

12-13 JULY 2007

Programme and Abstracts

National Association for the Relief of Paget's Disease *and the*
Botnar Research Centre, University of Oxford Institute of Musculoskeletal Sciences
www.paget.org.uk

ST CATHERINE'S COLLEGE • OXFORD, UK

CONTENTS

Advances in the Molecular Pharmacology and Therapeutics of Bone Disease

Advances in the Molecular Pharmacology and Therapeutics of Bone Disease AND International Symposium on Paget's Disease

Cover Image *'Dreaming Spires' Oxford.*

10–12 JULY 2007

Advances in the Molecular Pharmacology and Therapeutics of Bone Disease

St Catherine's College, Oxford

Scientific Committee:

Chairman: **Graham Russell** *(Oxford, UK)*

Matt Brown *(Oxford, UK & Brisbane, Australia)*

Jack Martin *(Melbourne, Australia)*

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FOR FURTHER INFORMATION:

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BRC

TUESDAY 10 JULY 2007

09:15 **Registration and coffee**

09:50 **Welcome**
Graham Russell *(Oxford, UK)*

10:00 **Cellular regulation of bone metabolism**
Chairs: **Jack Martin** *(Melbourne, Australia)* & **David Roodman** *(Pittsburgh, USA)*

10:00 S1 INTERACTIONS WITH THE IMMUNE SYSTEM IN THE REGULATION OF BONE FUNCTION
Matt Gillespie *(Melbourne, Australia)*

10:30 S2 THE ROLE OF OSTEOCYTES IN THE REGULATION OF BONE FUNCTION
Brendon Noble *(Edinburgh, UK)*

11:00 S3 BONE AS A METABOLIC REGULATOR
Patricia Ducy *(New York, USA)*

11:30 **Break**

11:45 **Anabolic agents for bone**
Chairs: **Greg Mundy** *(Nashville, USA)* & **Jonathan Reeve** *(Cambridge, UK)*

11:45 S4 PROGRESS WITH THE DEVELOPMENT OF ANABOLIC AGENTS FOR BONE
Roland Baron *(New Haven, USA)*

12:15 S5 UNDERSTANDING MECHANISMS OF THE ANABOLIC ACTION OF PTH
David Dempster *(West Haverstraw, USA)*

12:45 **Lunch**

14:00 **Novel regulators of bone**
Chairs: **Roger Francis** *(Newcastle upon Tyne, UK)* & **Michael Whyte** *(St Louis, USA)*

14:00 S6 STRONTIUM - MECHANISMS OF ACTION: EXPERIMENTAL AND CLINICAL EFFECTS
René Rizzoli *(Geneva, Switzerland)*

14:30 S7 IS THERE A FUTURE FOR VITAMIN D ANALOGUES IN OSTEOPOROSIS?
Roger Bouillon *(Leuven, Belgium)*

15:00 **Tea**

15:30 **Novel regulators of bone** *continued*
Chairs: **Matt Gillespie** *(Melbourne, Australia)* & **Mike Rogers** *(Aberdeen, UK)*

15:30 S8 CANNABINOIDS AND BONE: FRIEND OR FOE?
Aymen Idris *(Edinburgh, UK)*

15:50 S9 HYDROGEN ION SENSING
Tim Arnett *(London, UK)*

16:10 S10 PURINURGIC PATHWAYS
Jim Gallagher *(Liverpool, UK)*

16:30 S11 THYROID STIMULATING HORMONE (TSH) MAY SERVE AS A BONE ANABOLIC AGENT FOR POSTMENOPAUSAL OSTEOPOROSIS
Kuber Sampath *(Framingham, USA)*

16:50 S12 BONE MORPHOGENETIC PROTEINS IN 2007
Slobodan Vukicevic (*Zagreb, Croatia)*

17:20 **Close**

19:00 **Dinner**

20:15 **Oxford walking tour**

WEDNESDAY 11 JULY 2007

09:00 **Techniques and imaging**
Chairs: **Richard Eastell** *(Sheffield, UK)* & **Morten Karsdal** *(Herlev, Denmark)*

09:00 S13 STRUCTURAL GENOMICS AND DRUG DISCOVERY
Udo Oppermann *(Oxford, UK)*

09:30 S14 ADVANCES IN THE IMAGING OF BONE
Ralph Müller *(Zurich, Switzerland)*

10:00 S15 NEW APPROACHES TO GENETICS
Matt Brown *(Brisbane, Australia)*

10:30 S16 THE DEVELOPMENT OF MARKERS IN BONE
Jude Onyia *(Indianapolis, USA)*

11:00 **Coffee**

11:45 **New therapeutic areas and approaches**
Chairs: **Roger Bouillon** *(Leuven, Belgium)* & **Paul Wordsworth** *(Oxford, UK)*

11:45 S17 CURRENT THERAPIES IN INFLAMMATORY ARTHRITIS
Paul Emery *(Leeds, UK)*

12:15 S18 CURRENT CONCEPTS IN BONE ONCOLOGY AND THEIR THERAPEUTIC POTENTIAL
Greg Mundy *(Nashville, USA)*

12:45 **Lunch**

14:00 **New therapeutic areas and approaches** *continued*
Chairs: **Tim Arnett** *(London, UK)* & **Socrates Papapoulos** *(Leiden, Netherlands)*

14:00 S19 NHR (NUCLEAR HORMONE RECEPTOR) MODULATORS: SERMs, SARMs AND VITAMIN D
Henry Bryant *(Indianapolis, USA)*

14:30 S20 FROM THE DISCOVERY OF OPG AND RANKL TO THE PURSUIT OF SCLEROSTIN: MOLECULES REGULATING SKELETAL PHYSIOLOGY
Scott Simonet *(Thousand Oaks, USA)*

15:10 S21 THE RANK LIGAND SYSTEM: CLINICAL POTENTIAL
Nathalie Franchimont *(Zug, Switzerland)*

15:40 **Tea**

16:00 **New therapeutic areas and approaches** *continued*
Chairs: **Roland Baron** *(New Haven, USA)* & **Philippa Hulley** *(Oxford, UK)*

16:00 S22 NEW TARGETS FOR BONE ANABOLICS: SCLEROSTIN/SOST
Michaela Kneissel *(Basel, Switzerland)*

16:30 S23 VASCULAR CALCIFICATION: PATHOGENIC MECHANISMS AND OPPORTUNITIES FOR THERAPEUTIC INTERVENTION
Dwight Towler *(St Louis, USA)*

17:00 **Close**

19:30 **Reception and Dinner**

12-13 JULY 2007

Advances in the Molecular Pharmacology and Therapeutics of Bone Disease

AND

International Symposium on Paget's Disease

Joint Sessions

Scientific Committee:

Chairman: **Graham Russell** *(Oxford, UK)*
Michael Davie *(Oswestry, UK)*
Roger Francis *(Newcastle-upon-Tyne, UK)*
David Hosking *(Nottingham, UK)*
Anne Langston *(Aberdeen, UK)*
Stuart Ralston *(Edinburgh, UK)*
Peter Selby *(Manchester, UK)*

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FOR FURTHER INFORMATION:

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Paget's Disease

BRC

THURSDAY 12 JULY 2007

08:30 **Welcome and introduction**
Chairs: **Graham Russell** *(Oxford, UK)* & **Cyrus Cooper** *(Southampton, UK)*

08:40 S24 EVOLUTION OF TREATMENTS FOR PAGET'S DISEASE AND OSTEOPOROSIS
Paul Miller *(Lakewood, USA)*

09:10 **Bisphosphonate actions**
Chairs: **Hal Ebetino** *(Cincinnati, USA)* & **Greg Mundy** *(Nashville, USA)*

09:10 S25 MOLECULAR MECHANISMS OF ACTION OF BISPHOSPHONATES
Mike Rogers *(Aberdeen, UK)*

09:35 S26 ALTERNATE PATHWAYS OF ACTION OF BISPHOSPHONATES ON BONE CELLS
Teresita Bellido *(Little Rock, USA)*

10:00 S27 THE BIOLOGY OF GAMMA-DELTA T CELLS AND OPPORTUNITIES FOR PHARMACOLOGICAL INTERVENTION
Andrew Sewell *(Cardiff, UK)*

10:25 **Coffee**

10:50 **Therapeutic opportunities for bisphosphonates in osteoporosis and other disorders**
Chairs: **Peter Selby** *(Manchester, UK)* & **Ian Reid** *(Auckland, New Zealand)*

10:50 S28 EFFECT OF ZOLEDRONIC ACID 5 MG IV ONCE YEARLY ON HIP, SPINE, AND NON-SPINE FRACTURES IN PATIENTS WITH POSTMENOPAUSAL OSTEOPOROSIS
Richard Eastell *(Sheffield, UK)*

11:20 S29 HIP FRACTURE: WHAT ARE THE REASONS AND OPPORTUNITIES FOR PHARMACOLOGIC INTERVENTION?
Kenneth Lyles *(Durham, USA)*

11:50 S30 POTENTIAL ROLES OF BISPHOSPHONATES IN ORTHOPAEDIC APPLICATIONS
David Little *(Sydney, Australia)*

12:20 S31 POTENTIAL ROLES OF BISPHOSPHONATES IN OSTEOARTHRITIS
Roy Altman *(Miami, USA)*

12:50 **Lunch**

14:00 **Current controversies in bisphosphonate therapy**
Chairs: **Eugene McCloskey** *(Sheffield, UK)* & **Paul Miller** *(Lakewood, USA)*

14:00 S32 BISPHOSPHONATES AND OVERSUPPRESSION OF BONE TURNOVER: WEIGHING THE EVIDENCE
Socrates Papapoulos *(Leiden, Netherlands)*

14:30 S33 SEQUENTIAL TREATMENT OF BISPHOSPHONATES AND PTH: CHALLENGING CURRENT ASSUMPTIONS
Jürg Gasser *(Basel, Switzerland)*

15:00 S34 OSTEONECROSIS OF THE JAW AND BISPHOSPHONATES: AN UPDATE
Erik Eriksen *(Basle, Switzerland)*

15:30 **Tea**

THURSDAY 12 JULY 2007

16:00 **Oral Communications**

Chairs: **Erik Eriksen** *(Basle, Switzerland)* & **David Little** *(Sydney, Australia)*

16:00 P1 CIRCULATING CATHEPSIN K LEVELS BEFORE AND AFTER INTRAVENOUS BISPHOSPHONATE TREATMENT IN PAGET'S DISEASE OF BONE

V De Paola, L Gennari, D Merlotti, G Martini, F Valleggi, A Avanzati, M B Franci, M S Campagna, R Nuti

16:05 P2 EFFICACY AND SAFETY OF ZOLEDRONIC ACID IN PAGETS DISEASE OF BONE: 4 YEARS OF EXPERIENCE

A Conesa Mateos, D Rotés Sala, L Pérez Edo, J Carbonell Abelló

Department of Rheumatology. Hospital del Mar y Esperanza. Instituto Municipal de Asistencia Sanitaria (I.M.A.S). Universidad Autónoma. Barcelona, Spain

16:10 P3 IS PLAIN ABDOMINAL X-RAY A SENSITIVE TOOL FOR THE SCREENING OF PAGET'S DISEASE OF BONE?

L Corral-Gudino, J García-Aparicio, S Gómez-Castro, C A Montilla, J del Pino-Montes

Servicio de Reumatología. Hospital Universitario de Salmanca, Spain

16:15 P4 LONG-TERM EFFECTS OF SINGLE ZOLEDRONATE OR NERIDRONATE INFUSION IN PAGET'S DISEASE OF BONE

D Merlotti, L Gennari, F Valleggi, V De Paola, G Martini, A Avanzati, R Nuti

Department of Internal Medicine, Endocrine-Metabolic Sciences and Biochemistry, University of Siena, Italy

16:20 P5 MANAGEMENT OF PAGET'S DISEASE OF BONE: AN AUDIT OF CLINICAL PRACTICE IN AUSTRALIA

J P Walsh [1], R Attewell [2], M J Hooper [3], J D Wark [4], S Fletcher [5], V Ferrari [5], J A Eisman [6]

[1] Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [2] Covance Pty Ltd, Braddon, ACT, Australia; [3] Bone Research Program, ANZAC Research Institute, Concord Repatriation Hospital, The University of Sydney and Central Sydney Area Health Service, Sydney, NSW, Australia; [4] Department of Medicine, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia; [5] Novartis Pharmaceuticals Australia Pty Ltd, North Ryde, NSW, Australia; [6] Bone and Mineral Research Program, Garvan Institute of Medical Research, Sydney, NSW, Australia.

16:25 P6 RAPID PAIN RELIEF AND CLINICAL IMPROVEMENT WITH INTRAVENOUS ZOLEDRONIC ACID IN LOCALIZED TRANSIENT OSTEOPOROSIS OF THE HIP

J D Ringe, A Dorst, P Farahmand

Klinik 4 (Rheumatology, Osteology)Klinikum Leverkusen, University of Cologne, Germany

16:30 P7 TREATMENT OF HUNGARIAN PATIENTS WITH PAGET'S DISEASE OF BONE WITH ZOLEDRONIC ACID

J Donath, Zs Nagy, P Gergely Jr, Gy Poor

National Institute of Rheumatology and Physiotherapy, Budapest, Hungary

16:35 **Close**

19:00 **Dinner**

08:45 Epidemiology and genetics

Chairs: **Matt Brown** *(Brisbane, Australia)* & **Luigi Gennari** *(Siena, Italy)*

08:45 S35 UPDATE ON EPIDEMIOLOGY AND PATHOGENESIS OF PAGET'S DISEASE
Tim Cundy *(Auckland, New Zealand)*

09:15 S36 GENETIC BASIS OF PAGET'S DISEASE
Stuart Ralston *(Edinburgh, UK)*

09:45 S37 INCLUSION BODY MYOPATHY ASSOCIATED WITH PAGET'S DISEASE OF BONE AND/OR FRONTOTEMPORAL DEMENTIA
Virginia Kimonis *(Irvine, USA)*

10:15 Coffee

10:45 Epidemiology and genetics continued

Chairs: **Miep Helfrich** *(Aberdeen, UK)* & **Stuart Ralston** *(Edinburgh, UK)*

10:45 S38 GENETIC DISORDERS OF BONE TURNOVER, INCLUDING 'JUVENILE' PAGET'S DISEASE, AND THEIR MANAGEMENT
Michael Whyte *(St Louis, USA)*

11:15 Oral Communications

11:15 P8 A NOVEL MUTATION (P364S) UPSTREAM OF THE UBA DOMAIN IN SEQUESTOSOME 1/P62 ASSOCIATED WITH PAGET'S DISEASE WITH A MILD PHENOTYPE
J P Walsh [1,2], A L Magno [1,2,3], B K Ward [1,2,3], SL Rea [1,2,3], L Ward [1], J Xu [1,2,3]
[1] Department of Endocrinology & Diabetes, Sir Charles Gairdner Hospital, Nedlands, Australia; [2] School of Medicine & Pharmacology, University of Western Australia, Nedlands, Australia; [3] Western Australian Institute for Medical Research, Nedlands, Australia

11:20 P9 DISEASE-ASSOCIATED MUTATIONS IN THE SIGNAL PEPTIDE OF RANK ALTER RANK LOCALISATION AND DOWNSTREAM ACTIVATION OF NFKB.
J C Crockett [1], M Helfrich [1], J Greenhorn [1], D I Scott [1], A Duthie [1], S H Ralston [2], M J Rogers [1]
[1] Bone Research Group, University of Aberdeen, Aberdeen, United Kingdom; [2] Molecular Medicine Centre, University of Edinburgh, Edinburgh, United Kingdom

11:25 P10 EFFECT OF SQSTM1 MUTATIONS ON BONE CELLS IN VITRO
L J Hocking, M J Rogers
University of Aberdeen, Aberdeen, UK

11:30 P11 EFFECTS OF PAGET'S DISEASE OF BONE MUTATIONS ON THE UBIQUITIN-BINDING FUNCTION OF SQSTM1
D Najat [1], L Bradley [1], K Brownless [1], S Martin [1], A Falchetti [2], F Marini [2], M L Brandi [2], B Shaw [1], J R Cavey [1], R Layfield [1]
[1] University of Nottingham, UK; [2] University of Florence, Italy

11:35 P12 EVIDENCE OF ELEVATED ALP LEVELS IN CLINICALLY UNAFFECTED RELATIVES OF SUBJECTS WITH FAMILIAL PAGET'S DISEASE OF BONE
L Gennari, D Merlotti, V De Paola, F Valleggi, G Martini, A Avanzati, R Nuti
Department of Internal Medicine, Endocrine-Metabolic Sciences and Biochemistry, University of Siena, Italy

11:40 P13 IDENTIFICATION OF GENDER-SPECIFIC ASSOCIATION BETWEEN TNFRSF11B POLYMORPHISMS AND PAGET'S DISEASE OF BONE
G Beyens [1], A Daroszewska [2], F de Freitas [1], E Fransen [1], F Vanhoenacker [3], L Verbruggen [4], H Zmierczak [5], R Westhovens [6], J Van Offel [7], S H Ralston [2], J P Devogelaer [8], W Van Hul [1]
[1] Department of Medical Genetics, University and University Hospital of Antwerp, Belgium; [2] Molecular Medicine Centre, Western General Hospital, University of Edinburgh, United Kingdom; [3] Department of Radiology, University Hospital of Antwerp, Belgium; [4] Department of Rheumatology, University Hospital of Brussels, Belgium; [5] Unit of Osteoporosis and Metabolic Bone Diseases, University Hospital of Ghent, Belgium; [6] Department of Rheumatology, Catholic University of Leuven, Belgium; [7] Department of Immunology and Rheumatology, University Hospital of Antwerp, Belgium; [8] Department of Rheumatology, Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium

11:45 P14 MICE WITH A TRUNCATION MUTATION AFFECTING SQSTM1 EXHIBIT SEVERAL PHENOTYPIC FEATURES IN COMMON WITH PAGET'S DISEASE OF BONE.
J Rojas [1], A Daroszewska [1], M Helfrich [2], R Layfield [3], R van 't Hof [1], S Ralston [1]
[1] Molecular Medicine Centre, University of Edinburgh, Western General Hospital, Edinburgh, UK; [2] Medicine & Therapeutics, University of Aberdeen; [3] Institute of Neuroscience, University of Nottingham

11:50 P15 MUTATION AND HAPLOTYPE ANALYSIS OF THE SQSTM1 GENE IN BELGIAN PAGET'S DISEASE OF BONE PATIENTS
P Y J Chung [1], G Beyens [1], S Boonen [2], F E Offeciers [3], J Van Offel [4], R Westhovens [5], H Zmierczak [6], J P Devogelaer [7], W Van Hul [1]
[1] Department of Medical Genetics, University and University Hospital of Antwerp, Belgium; [2] Center for Metabolic Bone Diseases, University of Leuven, Belgium; [3] Univ. ENT Dept, AZ St Augustinus, Wilrijk, University of Antwerp, Belgium; [4] Department of Immunology and Rheumatology, University Hospital of Antwerp, Belgium; [5] Department of Rheumatology, Catholic University of Leuven, Belgium; [6] Unit of Osteoporosis and Metabolic Bone Diseases, University Hospital of Ghent, Belgium; [7] Department of Rheumatology, Saint-Luc University Hospital, Université Catholique de Louvain, Belgium

11:55 P16 PREVALENCE OF SQSTM1 MUTATIONS IN SALAMANCA, SPAIN
E Corral [1], L Corral-Gudino [2], J García-aparicio [2], C A Montilla [2], S Gómez-Castro [2], J del Pino Montes [2], R González-Sarmiento [1]
[1] Unidad de Medicina Molecular. Universidad de Salamanca; [2] Servicio de Reumaotología, Hospital Universitario de Salamanca, Spain

12:00 P17 SQSTM1 MUTATIONS AND PAGET'S DISEASE OF BONE - FUNCTIONAL AND STRUCTURAL STUDIES
R Layfield [1], J Long [1], J R Cavey [1], S Ralston [2], P W Sheppard [3], M S Searle [1]
[1] University of Nottingham, UK; [2] University of Edinburgh, UK; [3] BIOMOL International LP, Exeter, UK

12:05 Break

12:15 Clinical studies
Chairs: **Bill Fraser** *(Liverpool, UK)* & **Peter Selby** *(Manchester, UK)*

12:15 S39 WHAT HAVE WE LEARNED FROM THE PRISM STUDY?
Anne Langston *(Aberdeen, UK)*

12:45 Lunch and posters

14:00 Experimental studies
Chairs: **Nick Athanasou** *(Oxford, UK)* & **Tim Cundy** *(Auckland, New Zealand)*

14:00 S40 EXPERIMENTAL STUDIES IN PAGET'S DISEASE
David Roodman *(Pittsburgh, USA)*

14:30 S41 CELLULAR BIOLOGY IN PAGET'S DISEASE
Ian Reid *(Auckland, New Zealand)*

15:00 Oral communications - Experimental Studies
Chairs: **Jill Cornish** *(Auckland, New Zealand)* & **Roger Smith** *(Oxford, UK)*

15:00 P18 CANONICAL AND NON-CANONICAL MECHANISMS OF OSTEOCLAST FORMATION IN PAGET'S DISEASE OF BONE
F Jones, R Taylor, H Knowles, J Wass, N A Athanasou
Department of Pathology, Nuffield Orthopaedic Centre, Nuffield Department of Orthopaedic Surgery, University of Oxford, OX3 7LD

15:05 P19 P62 SIGNALING IN OSTEOCLASTS AND SURVIVAL PATHWAYS
E Chamoux [1], J Couture [1], J P Brown [2], S Roux [1]
Department of Rheumatology, [1] Sherbrooke University, Sherbrooke, [2] Laval University, Ste-Foy, PQ, Canada

15:10 P20 PAGET'S OSTEOSARCOMA IN SCOTLAND
S W Hamilton [1], E MacDuff [2], D E Boddie [1], T R Scotland [1], R Reid [2]
[1] Department of Orthopaedics, Woodend Hospital, Aberdeen; [2] Scottish Bone Tumour Registry, Western General Hospital, Glasgow

FRIDAY 13 JULY 2007

15:15 P21 ULTRASTRUCTURAL AND IMMUNOCYTOCHEMICAL CHARACTERISATION OF INCLUSIONS IN PAGET'S DISEASE AND RELATED DISORDERS
M H Helfrich [1], D I Scott [1], S Yuen [1], J Greenhorn [1], J C Crockett [1], L Hocking [1], S H Ralston [2], M J Rogers [1]
[1] University of Aberdeen, Aberdeen, UK; [2] University of Edinburgh, Edinburgh, UK

15:20 P22 UP-REGULATION OF THE INTERFERON SIGNALING PATHWAYS IN MONOCYTES FROM PATIENTS WITH PAGET'S DISEASE OF BONE
Z B Nagy, P Gergely Jr, J Donáth, G Poór
National Institute of Rheumatology and Physiotherapy, Budapest, Hungary

15:25 Break

15:30 Update on treatments in Paget's Disease
Chairs: **Michael Davie** *(Oswestry, UK)* & **Caje Moniz** *(London, UK)*

15:30 S42 ZOLEDRONIC ACID 5 MG IV IN THE TREATMENT OF PAGET'S DISEASE OF BONE
David Hosking *(Nottingham, UK)*

16:00 Tea and close

17:00 Keynote Lecture
Chairs: **Paul Miller** *(Oakwood, USA)* & **David Hosking** *(Nottingham, UK)*

17:00 THE PAGET FAMILY ACROSS THE GENERATIONS
Sir Julian Paget

17:30 Close

19:00 Dinner

SATURDAY 14 JULY 2007

PATIENTS' DAY

S1
INTERACTIONS WITH THE IMMUNE SYSTEM IN THE REGULATION OF BONE FUNCTION

Matthew Gillespie, *St Vincent's Institute of Medical Research, Victoria, Australia*

In determining the fundamental mechanisms of bone formation and resorption, most attention has been paid to the role of the either the osteoblast or osteoclast. It is well accepted that communication networks exist between these cells that are pivotal to the formation and activation of the osteoclast, and that the osteoclast also modulates osteoblast behaviour. However, studies into the action of cells of the immune system, particularly T, B and NK cells, to modulate the activity of either bone formation or resorption are in their infancy. These cells powerfully influence the growth and development of bone cells through the action of lymphocyte-derived cytokines. The most recognizable of these is Receptor Activator of NFkB Ligand (RANKL) that was original identified as a lymphocyte-derived factor that has profound effects upon the skeleton since it is absolutely required for osteoclast formation. RANKL is expressed by activated T lymphocytes and the primary role of activated T lymphocytes in inflammatory diseases such as arthritis to influence bone destruction through their production of TNFα and soluble RANKL is now accepted. The usefulness of immunosuppressive and anti-resorptive agents for the treatment of arthritis have been evaluated in animal models and appear to be promising. However on a cautionary note, nitrogen-containing bisphosphonates have the capacity to enhance the proliferation of some lymphocyte subsets that may exacerbate disease.

In addition to the role that lymphocytes play to promote osteoclast formation, several T cell-derived cytokines including IFN-γ, GM-CSF, IL-4, IL-10, IL-13, IL-23, osteoclast inhibitory lectin (OCIL), and secreted Frizzled-related proteins (sFRPs) act via lymphocytes or directly upon osteoclast precursors to inhibit osteoclast formation. In contrast, IL-6, IL-7 and IL-17 act to stimulate osteoclast formation. Whilst many of the studies addressing mechanism of action of these molecules have been restricted to cell-based assays, data is emerging for their role in animal models. In mice that have been genetically altered, several of these interleukins have been demonstrated to have a fundamental role in controlling bone development.

The repertoire of factors that act through T lymphocytes to modulate osteoclast formation and or activity will be extended, and future studies will be aimed to decipher the complex and overlapping effects of the many immune and hemopoietic cytokines.

S2
THE ROLE OF OSTEOCYTES IN THE REGULATION OF BONE FUNCTION

Brendon Noble, *The Scottish Centre for Regenerative Medicine, Edinburgh University, UK*

Osteocytes are the most abundant cell type in bone; however, they remain the least characterised of these. Several theories have been proposed regarding their function, including osteolysis, sensing the strains produced in response to mechanical loading of bones and producing signals that affect the function of osteoblasts and osteoclasts as well as the expression of molecules that directly affect the turnover process. This review also discusses the role of osteocyte apoptosis in targeted bone remodeling and proposes that the incidence of osteocyte apoptosis is in line with the description of apoptosis as an essential homeostatic mechanism for the healthy maintenance of tissues.

Inappropriate targeting of bone remodeling underlies a number of musculoskeletal disease states including Paget's disease and Osteoporosis. The mechanism driving the targeting of bone resorption is unknown. Our previous studies have demonstrated a close association between regions of bone containing apoptotic osteocytes and resorption surfaces in both healthy and pathological conditions. Such findings raise the possibility of a currently unknown causal signaling mechanism between the dying osteocyte and effector cells at the bone surface.

Identification of the specific signals implicated in this phenomenon and the method by which they are delivered will profoundly increase our understanding of the effector cell targeting system in bone providing a platform to production of novel intervention strategies.

S3
BONE AS A METABOLIC REGULATOR

Patricia Ducy *and* **Gerard Karsenty**, *Columbia University Medical center, New York, NY 10032. USA*

Besides its molecular complexity the regulation of bone remodeling by leptin raises the prospect that skeleton exerts a feedback control of energy homeostasis. To test this hypothesis we embarked on a genetic screen in mice looking for genes expressed in osteoblasts, encoding signaling molecules, and affecting energy metabolism. As a result we generated mice lacking the intracellular protein tyrosine phosphatase OST-PTP generally or specifically in osteoblasts. Both mutant mice display as their only phenotype a severe hypoglycemia secondary to an increase in insulin secretion and insulin sensitivity. Furthermore, OST-PTP deficient mice are paradoxically lean and protected from chemically- or diet-induced obesity and diabetes. Remarkably, mice lacking an osteoblast-specific secreted molecule termed BP display a mirror image phenotype i.e. they are glucose intolerant because of a decrease in insulin secretion and sensitivity. Genetic, biochemical and cell-based analyses

demonstrated that osteoblasts, via BP, stimulate pancreatic beta-cell proliferation and expression of Insulin and Adiponectin, an insulin-sensitizing adipokine. Analysis of OST-PTP deficient /BP heterozygous mutant mice demonstrated that these molecules lie in the same regulatory pathway and that OST-PTP metabolic phenotype is caused by a gain of function of BP bioactivity. By showing that a bone-derived secreted molecule regulates energy metabolism our results expand the spectrum of functions of skeleton, add further credence to the concept that bone and energy metabolisms regulate each other and raise the prospect that additional hormones regulating other aspects of energy metabolism may exist. Our observations also suggest that the pathogenesis of some degenerative diseases of energy metabolism may be more complex than anticipated.

S4

TARGETING THE WNT SIGNALING PATHWAY FOR OSTEOPOROSIS TREATMENT

Roland Baron, *Yale University School of Medicine, New Haven, CT, USA*

There is a strong medical need for a safe and effective anabolic treatment for osteopenic conditions such as osteoporosis or osteogenesis imperfecta. PTH is already on the market to treat severe osteoporosis, efficiently increasing bone mass more than a antiresorptive treatment. The fact that it is a large peptide requiring daily injections however makes it a very expensive and demanding therapeutic approach. Thus, cheaper and/or orally available anabolic therapies are a very high priority in drug discovery. The most important recent finding in anabolic approaches has been the identification of LRP5 and the Wnt signaling pathway as major regulators of bone mass in humans. Gain-of-function mutations in the LRP5 receptor in humans lead to the High Bone Mass (HBM) trait whereas loss-of-function mutations lead to the Osteoporosis Pseudo-Glioma (OPPG) syndrome. In mice, LRP5 gene deletion mimics the OPPG syndrome whereas the gain-of-function mutation mimics the HBM phenotype. Knockout of the closely related LRP6 receptor is embryonic lethal but mice heterozygote for LRP6 deletion (LRP6+/-) exhibit an osteopenic phenotype. Double mutants missing one allele of LRP6 and both alleles of LRP5 have a more severe osteoporotic phenotype than LRP5-/- mice, suggesting that both receptors participate, in part redundantly, in the regulation of bone mass. LRP5 and 6 are co-receptors with Frizzled for Wnt ligands. Wnt signaling leads to the inhibition of GSK3B, decreased phosphorylation of beta-catenin and activation of beta-catenin-dependent genes, including several osteoblast marker genes. Several targets involved in Wnt signaling are currently being explored for drug discovery: blocking the activity of endogenous antagonists of the pathway (Sclerostin, Dkk1, sFRPs), agonists of the LRP5 or LRP6 receptors and inhibitors of signaling events downstream of the LRP5/6 activation by Wnts (GSK3B inhibitors, LiCl) are all being explored as possible anabolic agents. These targets are also validated in mice: DKK1+/- mice show a marked increase in bone mass, sclerostin antibodies increase bone mass in rats, inhibition of GSK3beta activity by specific inhibitors or by Lithium chloride and targeted overexpression of a constitutively active beta Catenin all increase bone mass by activating Wnt signaling. Given the high level of basic and pharmaceutical research on this pathway for bone therapies, the field may be close to entering the first clinical trials where activation of the Wnt pathway will be tested in osteoporosis. A major question to address in preclinical studies remain safety issues linked to the reported link of Wnt family members with oncogenesis. However, the observations that some endogenous inhibitors are partially restricted to the bone microenvironment (Sost, Dkk1) suggest the possibility to increase Wnt signaling only in bone, avoiding side effects in other organs. Thus, activation of the Wnt pathway in bone currently remains the most promising approach to bone anabolic treatment.

S5

UNDERSTANDING MECHANISMS OF THE ANABOLIC ACTION OF PTH

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Anabolic agents, such as PTH, work by a fundamentally different cellular mechanism of action than antiresorptive agents. A more appropriate term for the latter would be "antiremodeling agents" because, although their initial effect is to lower resorption, they secondarily inhibit formation. Indeed, inhibition of remodeling is the primary mechanism by which this class of drugs works. By contrast, PTH treatment ultimately stimulates the bone remodeling rate and thereby stimulates net bone formation. With teriparatide treatment, the amount of bone laid down in each remodeling unit is increased, which is confirmed by an increase in osteon thickness. This distinguishes the effects of PTH treatment from other high-remodeling states, such as estrogen deficiency, which result in loss of bone structure and strength. The combination of an increase in the osteon thickness and an increase in the number of osteons being formed per unit time provides a mechanism for ongoing gains in the amount of bone tissue, including an increase in trabecular thickness. In addition to the stimulation of bone formation through this mechanism, referred to as "remodeling-based formation," there is also histomorphometric and biochemical evidence that, during the early stages of treatment, teriparatide stimulates formation directly, that is, without prior resorption. This is referred to as modeling-based formation and may occur by activation of lining cells on previously quiescent bone surfaces, or by osteoblasts that were engaged in remodeling-based formation annexing resting bone surfaces surrounding the resorption cavity (1). PTH treatment not only leads to

an increase trabecular thickness but also improves trabecular connectivity, as demonstrated by microcomputed tomography of iliac crest bone biopsies (2). The underlying mechanism for the improvement in trabecular connectivity is still unclear but may involve thickening of trabeculae followed by intratrabecular tunneling.

There was an early concern that PTH therapy might have a negative effect on cortical bone, with the notion that gains in cancellous bone may be achieved at the expense of cortical bone. This was not confirmed in animal studies, which showed that teriparatide improved cortical thickness and strength by stimulation of formation on both the endosteal and periosteal surfaces. Biopsy studies in humans also showed an increase in cortical thickness and stimulation of bone formation with a decrease in eroded perimeter on the endosteal surface (2). The concept that teriparatide is capable of stimulating periosteal bone formation and increasing bone diameter in humans remains controversial. However, there is recent histomorphometric evidence for stimulation of bone formation at the periosteal surface of the ilium following teriparatide treatment with an increase in tetracycline uptake and insulin-like growth factor expression on the periosteal surface (3). Thus, the 27 year-old belief that intermittent PTH treatment might be harmful to cortical bone appears to be losing ground. With that, however, comes the recognition that in order to assess the effects of PTH treatment in a clinical setting, we need to be careful when interpreting BMD changes, particularly areal measurements obtained by DXA.

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S6

STRONTIUM - MECHANISMS OF ACTION. EXPERIMENTAL AND CLINICAL EFFECTS

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Agents for the treatment of osteoporosis either decreased or increased bone turnover. The new drug strontium ranelate (SR) combines decreased bone resorption and maintained bone formation. Preclinical studies have shown an increase in ultimate strength of both vertebral body and long bones, with an increase in plastic energy. Thus, bone formed under SR treatment is able to withstand greater deformation before fracture, while possessing similar elastic properties as normal bone. 3D-microcomputerized tomography and histomorphometry analysis has demonstrated an improvement in trabecular (trabecular bone mass, connectivity, micro-geometry) and cortical (external diameter and cortical thickness) micro-architecture in animal treated with SR. There is no mineralization impairment. Nanoindentation of bony tissue requires a greater energy, indicating a change in intrinsic tissue quality under SR.

SR exerts antifracture efficacy whatever the severity of osteoporosis. SR significantly decreases the relative risk of new vertebral fracture by 48% in osteoporotic patients without prevalent vertebral fracture, and by 41% in patients with prevalent vertebral fracture, over 3 years. Furthermore, SR reduces the relative risk of clinical vertebral fracture by 52% as early as the first year of treatment.

SR also reduces the relative risk of all peripheral fractures by 16%, and the relative risk of hip fracture by 36% in patients aged 74 years or more, and with a femoral neck bone mineral density d -2.4 SD (NHANES III reference range). The efficacy of SR is also specifically demonstrated in the elderly (age e 80 years) with a significant reduction in both vertebral and peripheral fracture relative risks over 3 years (relative risk -32%; P=0.013, and -31%; P=0.011, respectively).

The antifracture efficacy is sustained with -24% and -18% reduction in vertebral and non-vertebral fracture, respectively, after 5 years of placebo-controlled study. In elderly older than 80 years, the corresponding fracture risk reductions were -31 and -26%.

SR is well tolerated and significantly improves patients' quality of life compared with the placebo group. SR is a efficacious and rapidly acting treatment for postmenopausal women with osteoporosis, with sustained (over 3 years, up to 5 years) vertebral and non-vertebral antifracture efficacy, whatever the severity of the disease.

S7

USE OF VITAMIN D ANALOGS FOR THE TREATMENT OF OSTEOPOROSIS

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Ligand activated VDR regulates about 3 % the mouse/human genome and has a wide variety of physiologic actions. It regulates calcium and bone homeostasis by increasing transepithelial calcium transport (intestine, kidney) and regulates the functions of bone and parathyroid cells. VDR.1±,25-(OH)2D3 also has major effects on many other target tissues as demonstrated in VDR KO mice and men.

VDR-1,25(OH)2D has dual actions on bone as it can stimulate osteoblast function as well as osteoclastogenesis. The natural hormone 1,25-(OH)2D and its precursor, 1±-OHD, have been used in the past with some beneficial effects on fracture prevalence of postmenopausal women and in glucocorticoid induced osteoporosis but their use is limited by a narrow therapeutic range. Some synthetic analogs of 1,25-(OH)2D, largely selected on the basis of trial and error analysis in animal models of osteoporosis, can increase bone mineral content and bone mineral density. This

increase in BMD can be massive when associated with mild hypercalcemia. Even in the absence of hypercalcemia and minimal or mild increase in urinary calcium excretion, the increase in BMC/BMD can exceed the effects of bisphosphonates.

The lead candidates in clinical (ED71) or preclinical development have divergent chemical structures. We have selected a nonsteriodal D ring analog capable to prevent or correct bone loss in primary or secondary mouse osteoporosis models (primary or secondary prevention of ovariectomy-induced bone loss). Such analog is also able to substantially increase trabecular and even cortical bone mass and density in gonad-intact mice. The mode of action (selective for bone) is not elucidated and seems to be different between different analogs. Apart from inhibition of resorption some selective vitamin D analogs can also increase bone formation rate, and therefore are true anabolic agents. Whether efficacy and safety windows observed in rodents will also apply to human awaits clinical studies.

S12
BONE MORPHOGENETIC PROTEINS IN 2007

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Currently, bone is the only human organ that can be fully regenerated by exogenously applied bone morphogenetic proteins (BMPs) when physiological mechanisms of fracture repair fail. More than 340.000 patients worldwide have been treated with recombinant BMPs for long bone non-unions, acute fractures and spinal fusions. Due to the controversial role of BMPs in tumor biology their use in patients with bone malignancies has been postponed. Recently, it has been shown that systemically administered BMP-7 inhibits breast and prostate cancer growth in the bone marrow of animal models through inhibiting transforming growth factor _-induced activation of Smad-2/-3 via ALK-5, and through inducing E-cadherin expression preserving the epithelial phenotype. By counteracting the epithelial-to-mesenchymal transition, BMP-7 prevents the acquisition of an invasive, metastatic phenotype. The unique ability to transform muscle into bone has been used to "pre-tailor" cranio-facial bones in the back muscles of patients. BMPs inhibit myogenesis and promote the formation of new bone through activating the expression of inhibitor of DNA binding (Id) genes. Id proteins then repress transcription by basic helix-loop-helix heterodymers containing myoD/myogenin which results in the inhibition of myogenesis and leads to the formation of osteoblasts. Apart from the local application of BMPs for the regeneration of bone, BMPs have also been used systemically to increase the volume of the skeleton, regenerate kidney, diminish vascular calcification and regulate glucose levels in serum. Partially overlapping expression patterns of BMPs during development and regeneration of the skeleton serve to modulate strength of BMP signaling rather than create discreet fields of ligands with intrinsically different signaling properties. Although diverse actions of BMPs have been extensively investigated, their redundancy and specificity, including availability in biological fluids remains to be explored.

S14
ADVANCES IN THE IMAGING OF BONE

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With recent advances in molecular medicine and disease treatment there is a strong need for quantitative image processing of three-dimensional bone structures in the context of bone quality assessment. A number of new microstructural imaging modalities have been put forward recently allowing quantification with high precision and accuracy. Although biomedical imaging technology is now readily available, few attempts have been made to expand the capabilities of these systems by adding quantitative analysis tools as an integrative part of biomedical information technology and by exploring structure function relationships in a hierarchical fashion over the different length scales. Nevertheless, such quantitative endpoints have become an important factor for success in basic research and the development of novel therapeutic strategies in biomedicine and clinical practice. Micro- and nano-computed tomography is key to these developments being an approach to image and quantify trabecular bone in three dimensions and providing multi-scale biological imaging capabilities with isotropic resolutions ranging from a few millimetre (clinical CT), to a few micrometers (μCT) down to one hundred nanometers (synchrotron radiation nanoCT). The technology is expected to shed light on the relationship between structural measures of bone quality and a certain diseases or therapies. As part of the presentation, new strategies for advanced hierarchical quantification of bone and their structure function relationship will be presented. The focus will be on aspects of bioengineering and biomedical information technology in hierarchical micro- and nano-imaging as well as image-guided biomechanics. In conclusion, microtomographic imaging is a nondestructive, noninvasive, and precise procedure that allows 3D assessment and computation of microstructural and micromechanical properties in basic science and clinical bone studies. The procedure can help improve predictions of bone failure, clarify the pathophysiology of skeletal diseases, and define the response to therapy. Hierarchical bioimaging in combination with biocomputational approaches are well suited to investigate quantitative structure function relationships to investigate aspects of bone quality. We expect these findings to improve our understanding of structure function relationships in bone and with that to also allow improved quality control and more successful

outcomes in studies dealing with pharmacological treatment of bone.

S16
THE DEVELOPMENT OF NEW MARKERS IN BONE

Jude Onyia, *Indianapolis, USA*

Bone strength is significantly dependent upon bone density, turnover and quality, including micro-architecture, mineralization, and geometry. To-date, bone mineral density (BMD) measurements play critical role in osteoporosis management. However, the extent to which BMD alone contribute to bone fragility, fracture risk and the therapeutic efficacy of osteoporosis drugs is controversial. Additional multi-parametric markers at the molecular level are clearly needed to truly capture/model bone strength and its complex relationships. This presentation will provide a review of our recent studies on the development of genomic and proteomic "signatures" relating to how osteoporosis therapies, impact bone strength and quality. We developed a novel "gene expression signature" consistent of bone, cartilage, adipogenic and other markers that predict sensitivity to bone building drugs in a preclinical osteopenia model. The results were validated with response to aging, disease progression, and drug treatment and predict and differentiate drug response. Furthermore, the molecular signature boosts predictive power when combined with a classical predictor such as BMD and contemplate new therapeutic strategies and opportunities for better use of existing drugs.

S17
THERAPIES IN INFLAMMATORY DISEASES

Paul Emery, *Leeds, UK*

Inflammatory arthritis of which rheumatoid arthritis is the prototype, is characterised by persistent inflammation of the synovial joints, with the release of cytokines causing local periarticular osteoporosis, boney erosions and systemic osteoporosis. Bony changes are recognised as the pathognomic feature of rheumatoid arthritis. Traditional therapies have been used more successfully to suppress inflammation and a certain number of patients will enter remission. Despite being in this state, structural damage still progresses, this led to the suggestion that there is an uncoupling of the processes of inflammation and damage.

Imaging has been used to document the progression of disease, assess the prognosis of the disorders, and document the impact of therapy. By allowing simultaneous imaging of synovitis and boney damage in patients in apparent remission, it has been possible to document sub-clinical synovitis and show that this correlates with subsequent boney damage. Thus, these data provide the explanation of why remission patients deteriorate.

The availability of new agents targeted at cytokines particularly TNF has been of great interest producing major improvements in symptoms and signs, and against initial expectations a marked inhibition of structural change. The impact of TNF blockade on the expression of RANKL directly and indirectly is the probable explanation. Furthermore, dominance of IL-1 in the pathogenesis of bony damage found in animal models has not been reproduced in humans.

Although TNF blockade has been extremely successful many patients fail therapy either due to toxicity or lack of efficacy. Furthermore, there are many contraindications. Thus, therapy which could target the systemic bone loss as well as the local bony erosions would be of great benefit. A mode of action study was undertaken with zoledronic acid in patients with early RA and demonstrated that not only could bone loss be prevented but that erosions were effectively terminated. The efficacy of TNF blockade and osteoclast inhibition provides a potential complementary therapeutic approach. Other therapies including B-cell depleting therapies and co-stimulatory blocking therapies have been examined at the tissue level as well as radiologically in patients, furthermore IL-6 receptor antibody is now in phase III studies.

S18
CANCER AND BONE

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The effects on bone caused by common malignancies such as breast cancer, prostate cancer and myeloma are becoming increasingly better recognized. As patients are living longer with these diseases, the importance of the skeletal complications is becoming progressively magnified. Recently, there has been a marked increase in our understanding of the cellular interactions which occur in the bone micro- environment between bone cells and normal host cells. These interactions involve not just the cancer cells, but also a myriad of host cells which become markedly altered in gene expression patterns and in behavior by the presence of the tumor. There are many similarities to the bone marrow niche which is responsible for the nurture and release of hematopoietic stem cells. Recently, there has been an increasing recognition of the importance of osteoblast differentiation in the behavior of tumor cells in the bone microenvironment. These cellular interactions and the mechanisms, as well as the clinical implications, will be discussed.

S20

FROM THE DISCOVERY OF OPG AND RANKL TO THE PURSUIT OF SCLEROSTIN: MOLECULES REGULATING SKELETAL PHYSIOLOGY

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The principal soluble regulator of bone resorption, osteoprotegerin (OPG), was identified through homology to the tumor necrosis factor receptor (TNFR) superfamily. Unlike other members of the TNFR class of proteins, the OPG transcript lacked a hydrophobic membrane-spanning sequence suggesting it was a novel secreted protein. In embryonic mice, OPG mRNA was prominently expressed in developing bone. Deletion of the OPG gene in mice produced severe osteoporosis, while transgenic (Tg) mice overexpressing OPG exhibited pronounced increases in bone density associated with a decrease in osteoclasts. Expression cloning revealed that OPG binds to receptor activator of NF-kappaB ligand (RANKL) and intervenes in the signalling pathway with its receptor, RANK. RANK activation is essential for osteoclast differentiation and bone resorption activity, as evidenced by Tg mice with RANKL deletion that are severely osteopetrotic. Subsequently, it was demonstrated that recombinant OPG treatment protected against bone loss in the oviarectomized (OVX) rat model of postmenopausal osteoporosis (PMO).

While the OPG/RANKL pathway is critical for osteoclastic bone resorption, the osteocyte-secreted protein sclerostin also plays a key role in controlling bone mass. Inherited OPG deficiency leads to juvenile Paget's disease, associated with excessive bone remodelling. Conversely, inherited sclerostin deficiency in humans results in the condition sclerosteosis, characterized by progressive bone thickening due to increased bone formation without increased bone resorption. This anabolic effect is due to the loss of the ability of sclerostin to inhibit osteoblastic activity.

Both of these pathways are therefore possible targets for intervention in bone disorders characterized by osteopenia. Anti RANKL and anti sclerostin monoclonal antibodies represent a novel and promising approach in the treatment of human osteoporotic bone disorders.

S21

THE RANK LIGAND SYSTEM - CLINICAL POTENTIAL

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Receptor activator of NF-kappaB ligand (RANKL) is the primary regulator of osteoclast activity and skeletal remodelling. Its signalling action is blocked by the soluble receptor osteoprotegerin (OPG), thereby inhibiting osteoclast maturation and activity. In an ovariectomized rat model of postmenopausal osteoporosis (PMO), inhibition of RANKL by OPG increased bone mineral density (BMD) and bone strength. Similarly, suppression of bone resorption and increase in radial bone mass was observed after OPG treatment of 2 adult patients with juvenile Paget's disease (Cundy, 2005). Also, based on preclinical and clinical data, RANKL inhibition prevents bone loss associated with cancer, and bone loss and bone erosions in rheumatoid arthritis. Denosumab, a fully human monoclonal antibody that inhibits RANKL, increased cortical bone area and mineral content in non-human primates, improving bone strength. Results from a phase 2 study of postmenopausal women treated with denosumab for 2 years are presented.

A multi-center, randomized, double-blind, phase 2 study enrolled healthy postmenopausal women with low BMD, not currently on bone metabolism-altering therapy. Subjects received denosumab 6, 14, or 30 mg SC every 3 months or, 14, 60, 100, or 210 mg SC every 6 months. Control arms received placebo or oral open-label alendronate (ALN). The 12-month primary endpoint, percent change in BMD of the lumbar spine, is presented along with 24-month data from other sites.

Of 412 women enrolled, 337 completed 24 months of study (259 denosumab, 38 placebo, 40 ALN). After 24 months, subjects treated with denosumab had significantly greater increases in BMD compared to placebo ($P < .001$). Denosumab treatment also significantly suppressed the bone turnover markers urine N-telopeptide (uNTx)/creatinine and serum C-telopeptide (sCTx) compared with placebo ($P < .001$). The number and severity of the adverse events was similar among all treatment groups, with the most common adverse events being upper respiratory tract infection and arthralgia. No neutralizing antibodies were observed over the 24-month treatment period.

In postmenopausal women with low BMD, anti-RANKL treatment with denosumab for 24 months produced significant increases in BMD, and sustained, significant decreases in bone turnover markers from baseline compared with placebo. Ongoing phase 3 studies are evaluating denosumab, administered twice a year, for the prevention and treatment of PMO.

S22

MULTIPLE PATHS TO TARGET SOST FOR OSTEOPOROSIS THERAPY

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SOST encodes for the secreted glycoprotein sclerostin - a potent osteocyte secreted negative regulator of bone formation. Lack of sclerostin expression gives rise to sclerosteosis [MIM 269500]. Patients suffer from life-long bone overgrowth resulting in increased bone mass and strength. This phenotype can be recapitulated in sclerostin

deficient mice and sclerostin overexpression results in osteopenia. Antibodies can neutralize sclerostin inhibitory action on bone formation in vitro and in vivo. Hence understanding regulation and action of such a key controller of bone mass should result in the discovery of novel approaches for osteoporosis therapy.

We found in collaboration with G. Loots [Berkley Livermore] that a distant enhancer element drives SOST expression in bone. In vitro and in vivo studies demontrate that the enhancer element mediates SOST responsiveness to bone forming parathyroid hormone. We utilized this knowledge to interrogate our compound libraries for SOST expression inhibitors with a reporter bone cell line. Several hit classes were identified and upstream target identification could be achieved by siRNA mediated knockdown experiments. One identified target class is PDE4A. Repression of the cAMP degrading action of PDE4A inhibits SOST - consistent with the observation that SOST is down-regulated by parathyroid hormone in a cAMP dependent manner. Modulation of some of the discovered target classes increases bone mass in vivo in long-term experiments in aged rats.

Identification of low molecular weight sclerostin inhibitors is hampered by the fact that sclerostin is in vitro flexibly folded, with a structured core. This suggests that sclerostin folds upon binding to its interaction partners. Sclerostin has inhibitory effects in vitro on Wnt and BMP signaling pathways, but it is not entirely understood how sclerostin mediates its action in vivo. We pursued hence a proteomics approach to identify sclerostin interaction partners utilizing the two sclerostin expressing cell lines UMR-106 and HEK293. This approach yielded LRP6 as a known interaction partner together with novel sclerostin interaction partners. Overexpression and siRNA experiments confirm a sclerostin enhancing action in vitro identifying them as putative new targets for osteoporosis therapy.

S23

VASCULAR CALCIFICATION: PATHOGENIC MECHANISMS AND OPPORTUNITIES FOR THERAPEUTIC INTERVENTION

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The second most frequent mineralized structure in the human body is the arterial vasculature. Once considered a passive process, arterial calcification has emerged as an actively regulated form of matrix calcium metabolism. At least four distinct histoanatomic types of vascular calcification exist. Atherosclerotic intimal calcification (Vb plaque) is characterized by an eccentric, lumen-deforming fibrous arterial lesion with sub-intimal cholesterol deposits and mineralizing apoptotic bodies immediately juxtaposed to calcifying vascular cells (CVCs). The CVC -- a pericyte-like myofibroblast -- elaborates osteo-/chondrogenic gene regulatory programs that promote additional calcium accrual. Oxysterols derived from LDL cholesterol activate CVC-dependent mineralization. Medial artery calcification (MAC) stiffens but does not occlude vessels, characterized by elastinolysis and circumferential matrix vesicle - dependent calcification with much less collagen deposition. Diabetes and uremia most commonly promote MAC. Msx2-Wnt osteogenic programs that control craniofacial mineralization are ectopically activated in aortic tissues. Low-grade systemic inflammation upregulates aortic adventitial Msx2 expression, generating paracrine Wnt signals that program mural CVCs to express alkaline phosphatase (ALP). Elevate calcium-phosphate levels of uremia enhance matrix vesicle formation and mineralization. In aortic valve calcification, interstitial valve myofibroblasts behave like CVCs, elaborating osteogenic programs in response to mechanical, inflammatory, and dysmetabolic stimuli. At initiation, aortic valve calcification is clearly osteogenic and cell-mediated; however, with advanced disease, calcified valves either remodel to form lamellar bone (cell-mediated) or accumulate mineral via epitaxial deposition of amorphous calcium phosphate. Aortic valve calcification progresses as components of metabolic syndrome accrue. Calcific uremic arteriolopathy (CUA) -calciphylaxis - is a mercifully uncommon form of medial calcification of dermal, pulmonary, and mesenteric arterioles, with intimal fibroproliferative occlusion that causes tissue necrosis. CUA arises in the setting of severe renal insufficiency and anticoagulation with coumadin. Inflammatory redox signals that upregulate arterial ALP and compromise tissue defenses to ectopic mineral deposition (tissue pyrophosphate levels, hepatic fetuin expression, arterial matrix Gla protein function) are common to all forms of macrovascular calcification. A better understanding of disease biology will lead to novel strategies to reduce vascular calcium accrual - and help ameliorate costly burdens of stroke, foot amputation, vascular dementia, and cardiac disease.

S25

MOLECULAR MECHANISMS OF ACTION OF BISPHOSPHONATES

Michael J Rogers. *Bone & Musculoskeletal Programme, Institute of Medical Sciences, University of Aberdeen, Aberdeen UK*

Bisphosphonates are well-established and effective drugs for the treatment of osteoporosis, Paget's disease and cancer-associated bone disease. The molecular mechanisms by which these agents inhibit bone destruction have recently been identified; following binding to bone then release and uptake by osteoclasts in vivo, simple bisphosphonates are metabolized intracellularly to cytotoxic analogues of ATP whereas nitrogen-containing bisphosphonates (N-BPs) inhibit the enzyme FPP synthase, thereby preventing the prenylation of small GTPase proteins that subsequently accumulate in

their unprenylated form. Recent studies suggest that unprenylated small GTPases may inhibit osteoclast function via inappropriate and sustained activation of downstream signalling pathways.

The exact manner in which N-BPs inhibit FPP synthase is just becoming clear. The recent generation of x-ray crystal structures of the human FPP synthase enzyme, co-crystallised with N-BPs, indicates that the drugs appear to bind in one of the two isoprenoid binding pockets (that would normally bind GPP), with the R2 side chain positioned in a hydrophobic cleft, and the phosphonate groups bound to a cluster of magnesium ions. Interestingly, the nitrogen atom in the side chain appears to form hydrogen bonds with a critical, conserved threonine and lysine residue. Hence, N-BPs mimick the structure of the enzyme's natural isoprenoid pyrophosphate substrates and act as carbocation transition state analogues. Enzyme kinetic analysis with human FPP synthase also indicates that the interaction with N-BPs is highly complex and characteristic of "slow-tight binding" inhibition, involving conformational changes in the structure of the enzyme. These studies are therefore beginning to provide new insights, at the detailed molecular level, into the reasons why minor changes to the structure of the N-BP side chain or to the phosphonate groups markedly influence the potency for inhibiting FPP synthase and hence bone resorption. In addition, minor changes to the structure of N-BPs can create compounds that inhibit other enzymes of the mevalonate pathway, thereby specifically preventing the prenylation of only certain small GTPases. Such novel analogues also have anti-resorptive and anti-tumour activity in vitro and could give rise to new classes of pharmacologic agents.

S26
ALTERNATIVE PATHWAYS OF ACTION OF BISPHOSPHONATES IN BONE CELLS

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A well-established effect of bisphosphonates on bone is inhibition of resorption due to decreased osteoclast progenitor development, decreased osteoclast recruitment, and promotion of apoptosis of mature osteoclasts. Recent evidence demonstrates that, in addition, bisphosphonates inhibits apoptosis of osteoblasts and osteocytes and that this action requires expression of connexin 43 (Cx43). Delayed osteoblast apoptosis may increase the osteoblast work time increasing trabecular thickness; whereas preservation of osteocytes may contribute to the anti-fracture efficacy of bisphosphonates, which is disproportional to their effect on BMD. Mechanistic studies showed that inhibition of osteoblast and osteocyte apoptosis requires opening of Cx43 hemichannels and activation of the extracellular signal regulated kinases ERKs by bisphosphonates. Remarkably, unlike most ERK activators, bisphosphonates do not induce ERK nuclear accumulation but instead ERKs accumulate in the cytoplasm where phosphorylate molecules that promote survival. Retention of bisphosphonate-activated ERKs outside the nucleus is due to their association with Cx43, β-arrestin (a molecule that mediates internalization of G protein-coupled receptors and their cross-talk with MAP kinases) and clathrin (which mediates the internalization of membrane-associated proteins). The formation of this complex is required for bisphosphonate-induced extra-nuclear confinement of ERKs and anti-apoptosis on osteocytes. While all bisphosphonates studied activate the Cx43/ β-arrestin/ERK pathway and prevent osteoblast and osteocyte survival, some do not induce osteoclast apoptosis or decrease remodeling. The latter analogs represent useful tools for dissecting the contribution of inhibition of osteoblast and osteocyte apoptosis to the beneficial effects of bisphosphonates and constitute a potential treatment for bone fragility in conditions in which decreased bone remodeling is not desirable.

S27
THE BIOLOGY OF GAMMA-DELTA T CELLS AND OPPORTUNITIES FOR PHARMACOLOGICAL INTERVENTION

Andrew Sewell, *Cardiff, UK*

γδ T cells form an important part of the adaptive immune response. Surprisingly, the ligands recognized by γδ T cell receptors (TCRs) and the exact biological function of the cells that express this receptor remain unclear. Recent research has linked these enigmatic cells to some of the side effects of bisphosphonates and provided opportunities for extending the use of these drugs.

Bisphosphonates, and in particular the aminobisphosphonates (nBPs), are known to have a number of side effects including a rise in body temperature and accompanying flu-like symptoms that resemble a typical acute phase response (APR). The mechanism for this

response has been partially elucidated and appears to be associated with the release of tumour necrosis factor (TNF)δ and interleukin (IL)6, although the effector cells that release these cytokines and the mechanism of action have been unclear. Our work has highlighted that the nBP-induced APR differs from the typical APR in that CD14+ cells such as monocytes and macrophages are not the primary cytokine producing cells. We have demonstrated that by inhibiting the mevalonate pathway, nBPs induce rapid and copious production of TNFδ and IL6 by peripheral blood γδT cells. Prior treatment with statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, blocks nBP-induced production of these proinflammatory cytokines by γδ T cells and may offer a means of avoiding the associated APR. Importantly, these findings may provide a further

mechanism for the anti-inflammatory effects attributed to inhibitors of HMG CoA reductase.

It is well established that γδ T cells act as a natural component of resistance to cutaneous carcinogenesis in mice. In humans it is known that γδ T cells exhibit potent Major histocompatibility complex-unrestricted cytotoxic activity in vitro against a wide range of tumour cell lines. Accordingly, there is increasing interest in the use of γδT cell-based immunotherapy in cancer. Recent clinical trials have concluded that nBPs could provide part of a novel, safe, efficacious and feasible means to increase the life-span of those with late stage metastaic tumours thereby extending the window of availability for other tumour-specific interventions.

S28

EFFECT OF ZOLEDRONIC ACID 5 MG IV ONCE YEARLY ON HIP, SPINE, AND NON-SPINE FRACTURES IN PATIENTS WITH POSTMENOPAUSAL OSTEOPOROSIS

Richard Eastell, *University of Sheffield, UK*

OBJECTIVES AND METHODS: The HORIZON-PFT is a multinational, 3-year, randomized, double-blind, placebo-controlled trial evaluating the potential of once-yearly zoledronic acid (ZOL) 5 mg, infused over 15 minutes, to decrease risk of fracture in 7736 postmenopausal osteoporotic women 65-89 years of age.

RESULTS: Treatment with ZOL 5 mg resulted in significant relative risk reductions in morphometric vertebral fracture of 70% vs PBO (3.8% vs 12.8%; 95% CI [62%, 76%]) and in hip fracture of 41% vs PBO (1.4% vs 2.5%; 95% CI [17%, 58%]). Secondary endpoints, non-vertebral (excluding finger, toe, and facial), clinical vertebral, and any clinical fracture (including non-vertebral, hip, and clinical vertebral), were significantly reduced by 25%, 77%, and 33% (all $P < .001$), respectively. Bone mineral density increased significantly in ZOL vs PBO at total hip (6.0%), lumbar spine (6.9%) and femoral neck (5.0%) ($P < .0001$). While transient increases in serum creatinine ≥0.5 mg/dL over pre-infusion levels were seen in a small fraction (1.3%) of patients in the ZOL 5 mg group; no cumulative impact on renal function was demonstrable. Hypocalcemia (serum calcium < 2.075 mmol/L) was observed in 2.3% of patients. Virtually all events occurred after the first infusion of ZOL, and all cases were asymptomatic and transient. Adverse events occurring ≤3 days after infusion were more frequent after first infusion (44.7% ZOL vs 14.7% PBO) but declined markedly on subsequent infusions. There were more atrial fibrillation serious adverse events in ZOL vs PBO (1.3% vs 0.5%). Two cases of osteonecrosis of the jaw (1 in PBO, 1 in ZOL) were confirmed with adjudication; both cases resolved with antibiotic therapy and limited debridement.

CONCLUSIONS: Once-yearly infusion of ZOL 5mg over 3 years achieves a highly significant decrease in vertebral, hip, and other fracture risk and is generally safe and well tolerated.

S29

HIP FRACTURE: WHAT ARE THE REASONS AND OPPORTUNITIES FOR PHARMACOLOGIC INTERVENTION?

Kenneth W Lyles, *Duke University Medical Center, VA Medical Center, Durham, NC, USA*

Hip fractures

Incidence of hip fractures is expected to double over the next 50 years.

The mortality risk with hip fracture is equal to or greater than mortality risk associated with some cancers (eg, breast, endometrial). Mortality rate of approximately 20% 1 year following hip fracture. Patients with hip fractures are different from women with vertebral fractures: one third are male; more functional impairments; lower life expectancy and more co-morbidity; and great fall risk and more mobility impairment. Studies of peri- and postmenopausal women with prior fractures had 2.0 (95% CI=1.8,2.1) times the risk of subsequent fracture compared with women without prior fractures. For other studies (including men and women of all ages), the risk was increased by 2.2 (1.9, 2.6) times. Patients with osteoporotic fractures (vertebra, distal forearm and hip) are not evaluated for osteoporosis and do not receive therapy for their disease. In summary, hip fractures are common and cause disability and increase mortality. They are associated with an increased risk of subsequent fractures. They are not treated with osteoporosis medications to reduce the risk of subsequent fractures. When there are data showing that with therapy can reduce the rate of subsequent fracture, do we know how to get patients treated?

S30

POTENTIAL ROLES OF BISPHOSPHONATES IN ORTHOPAEDIC APPLICATIONS

David Little, *Sydney, Australia*

Bisphosphonates are used extensively bone disorders such as Paget's disease and osteoporosis and in the bone oncology field. Early indications are that roles for nitrogen-containing bisphosphonates (N-BPs) can also be found in the field of orthopaedic surgery, specifically in the modulation of bone repair.

As in metabolic bone disease, bone repair consists of anabolic and catabolic responses. It is possible to manipulate the anabolic and catabolic responses by pharmacologic means. We have shown that in pre-clinical models of distraction osteogenesis, bolus dosing with zoledronic acid can increase the amount and strength of the regenerate bone. Detailed analysis reveals that this is

via anti-catabolic means, with the anabolic response able to produce more net callus with catabolism inhibited. Similar pre-clinical trials underway in fracture healing indicate that while continuous and bolus dosing of zoledronic acid significantly increase the strength of healing, continuous treatment has a more adverse effect on remodeling. These studies show also that post-operative timing of the bolus dose results in increases in strength.

Osteonecrosis is another area under intense investigation. Although osteonecrosis comes in many varied forms, a common thread is bone resorption and joint destruction. The anti-catabolic effects of N-BPs have been shown to be beneficial in multiple pre-clinical and emerging clinical studies are also positive.

Joint arthroplasty is plagued by the problem of peri-prosthetic osteolysis. Prosthetic osteolysis and the improvement of initial prosthetic stability are also indications emerging from pre-clinical studies. It is known that the life of the prosthesis can be predicted in many cases from early migration. N-BPs have been shown to enhance the response in the periprosthetic region and increase ingrowth in pre-clinical studies. Investigation of locally delivered BP via the prosthesis is also ongoing. Early physician-initiated clinical trials have begun in this area, the first of which shows increased stability can be achieved with N-BPs.

Successful clinical trials of the bone morphogenetic proteins have opened the eyes of orthopaedic surgeons to the possibility of pharmacological interventions in bone repair. We have shown that combination therapy with BMPs and zoledronic acid out-performs either therapy alone in the healing of segmental defects in rodents. As the body of pre-clinical evidence continues to build, clinical trials are required to assess the potential of N-BPs and possibly other anti-catabolic molecules in the modulation of bone repair.

S31
BISPHOSPHONATES AND OSTEOARTHRITIS

Roy D Altman, *UCLA, Los Angeles, California, USA*

Present day therapy of osteoarthritis (OA) is symptomatic as there are no generally accepted disease (structure) modifying agents. Since bisphosphonates (BP) have a dramatic influence on bone metabolism with suggestive effects on cartilage, they are of potential interest in modifying progressive changes in OA.

The effects of BP on articular cartilage is not well understood. Biochemically, there is a suggestion that BP can alter chondrocyte metabolism with reduced chondrocyte apoptosis, altered metalloproteinase activity and more robust proteoglycans. In preclinical trials of inflammatory arthritis, there is a dip in release of inflammatory mediators. Yet, in human cartilage explants, there was no effect on IL-6 and IL-8 mediated joint destruction. Animal models, though limited, support a structure modifying role, particularly when the dose of the BP is high. There are reduced biomarkers of abnormal cartilage metabolism, e.g., type II collagen breakdown. Although subchondral bone and calcified cartilage become somewhat stable, marginal osteophytes developed in some of the preclinical models..

There are limited human trials of BP in OA. The results of a large 2 year study of risedronate in knee OA failed to demonstrate any clinical or radiographic benefit vs placebo, even though biomarkers of cartilage breakdown were reduced (Bingham et al, Arthritis Rheum 2006;54:3494). Even sensitive MRI measures of cartilage failed to show a benefit. In contrast, a smaller 1 year study (BRISK) demonstrated symptom improvement with a trend toward reduced knee joint space narrowing (Spector et al Arthritis Res Ther 2005;7:R625).

There is limited information on which BP may be more effective. At present, the nitrogen containing BP have been used in the most successful preclinical trials.

It is proposed that there is potential for BP in structure modification of OA. it appears that more preclinical research is needed on mechanism of action of BP on cartilage. It is possible that a lack of benefit from the existing clinical trials may relate to the limitation of the instruments used to measure clinical OA and progression of OA, with inadequate dosing of the BP.

S32
BISPHOSPHONATES AND "OVERSUPPRESSION" OF BONE TURNOVER: WEIGHING THE EVIDENCE

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The primary pharmacological action of bisphosphonates (BP) is the reduction of bone resorption and bone turnover to a level that is kept constant throughout the period of treatment, up to 10 years in controlled studies in osteoporosis. There have been concerns that this action, which is primarily responsible for the maintenance or increase in bone strength, may also compromise bone integrity, if suppression of bone turnover is excessive, leading to increased bone fragility. Numerous studies in different animal models with N-BPs given at a wide range of doses and time intervals have consistently shown maintenance or improvement in bone strength. The same was also the case in studies that reported microdamage accumulation in bones of normal dogs treated with N-BPs that showed, in addition, no relation between microdamage accumulation and mechanical properties of bone. In human controlled studies, the higher the suppression of bone turnover by BP the greater the reduction of the risk of non-vertebral fractures, including those of the hip and bone biopsies taken from osteoporotic patients treated for 5 and 10

years with BP showed no signs of abnormal bone metabolism. Finally, there was no increase in the risk of non-vertebral fractures in patients treated for up to 10 years with alendronate compared to those treated for 3 or 5 years,. In addition, bone turnover increased following discontinuation of BP therapy and bone exposed to bisphosphonate responds to PTH administration. Against this evidence are case studies showing unusual nonspine fractures in alendronate-treated patients associated with severely depressed bone formation, histologically assessed. Thus, the bulk of evidence indicates that suppression of bone turnover by BP, at the doses used in the treatment of postmenopausal osteoporosis, protects bone integrity and has no adverse consequences on bone strength. Issues related to the level of bone remodeling necessary for optimal bone health and potential risk factors that may contribute to bone fragility in patients treated with BPs need to be considered.

S33
SEQUENTIAL TREATMENTS OF BISPHOSPHONATES AND PTH: CHALLENGING CURRENT ASSUMPTIONS

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Chronic exposure to the bisphosphonate alendronate (ALN) has been shown to reduce the bone anabolic response to parathyroid hormone (PTH) in rats (Gasser JA, J Musculoskel Neuron Interact 2000;1:53) and humans (Finkelstein JA, N Engl J Med 2003;349:1216). In the classical view, osteoblasts (Obs) are not regarded as a primary target for bisphosphonates (BPs). However, recent data indicates that BP-induced inhibition of farnesyl pyrophosphate (FPP) synthase in Obs may explain the diminished bone anabolic response to PTH.

Groups of 10 skeletally mature Wistar rats were treated subcutaneously (SC) 3 times per week with vehicle or with equipotent doses of zoledronic acid (ZOL, 4 µg/kg), ibandronate (IBN, 10 µg/kg,) risedronate (RIS, 20 µg/kg), or ALN (40 µg/kg) for 8 weeks. Additional groups were treated with a single intravenous (IV) dose of 100 µg/kg ZOL, 250 µg/kg IBN, 500 µg/kg RIS, or 1000 µg/kg ALN. The total cumulative doses of the SC and IV BP-regimens were identical. Following BP-pretreatment, all animals were challenged with daily SC injections of 20 µg/kg/day hPTH(1-34) for 10 weeks and anabolic response was measured every 2 weeks by serial quantitative computed tomography of the proximal tibial metaphysis.

Results suggest that the response to PTH was reduced significantly in rats after chronic SC, but not single IV, administration of the 4 BPs, as indicated by total and cancellous bone mineral density (BMD), cortical thickness, and endocortical expansion. The effect was coincident with the early stage of the anabolic bone response during which PTH activates flat bone-lining cells into cuboid, collagen-synthesizing Obs. Together with our previous results, these data suggest, that chronic BP exposure results in their uptake into bone-lining cells, possibly by fluid endocytosis, and the accumulation of these non-metabolizable compounds at levels sufficient to interfere with protein prenylation (cytoskeletal function). As a result, this may reduce the ability of PTH to activate bone-lining cells into matrix-secreting Obs, a crucial step in the early bone anabolic response to PTH where these cells have to undergo a shape change. The inefficient uptake mechanism for BPs into Obs may explain, why this 'blunting' effect is only observed after chronic- but not infrequent administration in rats. If a similar mechanism is responsible for the clinically observed BP-PTH interaction, their infrequent dosing may allow to restore the full benefit of the bone anabolic response to PTH.

S34
OSTEONECROSIS OF THE JAW

Erik Fink Eriksen, *Novartis Pharma Basel*

Osteonecrosis of the jaw is a poorly defined condition, which is primarily defined by the presence of exposed bone in the oral cavity lasting more than 6-8 weeks. The most common symptoms are pain, heavy jaw feeling. Rare cases of extensive lesions involving most of the mandible have been reported. No uniform diagnostic criteria have been devised yet, which hampers research on epidemiology, pathogenesis and treatment of the disease. Right from the first studies reporting ONJ being associated with bisphosphonates in oncology patients, virtually all data on incidence and prevalence of ONJ stems from retrospective studies of poorly defined, mostly small cohorts. A retrospective review of 4000 cancer patients receiving iv bisphosphonates estimated an incidence of 0.8%, with the vast majority of cases affecting patients treated for myeloma or breast cancer. However, due to differences in classification, diagnostic uncertainties and ascertainment bias, estimates among oncology patients up to 10% have been quoted. The risk of ONJ seems much lower in populations receiving bisphosphonates for non-oncology indications (e.g. osteoporosis or Pagets disease), where several studies have reported similar risk estimates of less than 1/100,000. The only prospective adjudicated analysis of patients (N=7736) treated with zoledronic acid found 1 patient meeting adjudication criteria in the treatment group and 1 in placebo.

The pathogenesis is also poorly defined. Exposed bone in the oral cavity has previously been associated with cocaine abuse, herpes infections and phosphate overexposure ("phossy-jaw") and squamous cell carcinoma, local metastasis, Bechet`s disease constitute other differential diagnoses. Two main hypotheses have been put forward in explain the association between bisphosphonate use and ONJ . One focuses on bisphosphonate induced low turnover in bone eliciting a

vicious cycle leading to exposed bone and infection (inside-out process). The other main hypothesis focuses on anti-angiogenesis from combined therapy with cytostatics, steroids and bisphosphonates causing poor mucosal wound healing leading to exposed bone and subsequent infection in immuno-compromised patients (outside-in process). Vitamin D deficiency and diabetes have also been associated with ONJ, as has chronic actinomyces infection.

The treatment of ONJ is conservative focusing on antibiotic therapy and oral rinses, which generally lead to less pain and limit infection. However the antibiotic regimens recommended vary widely. Extensive surgery beyond local debridement of sequestra is generally not indicated as it may worsen the situation. Hyperbaric oxygen and ozone therapy have also been associated with some cases of healing.

S35
AN UPDATE ON THE EPIDEMIOLOGY AND PATHOGENESIS OF PAGET'S DISEASE

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Paget's disease remains unique amongst metabolic bone disease in that despite having highly effective medication, the aetiology of the disease remains mysterious. The enigmatic features include its more-or-less simultaneous appearance at multiple skeletal sites, its geographic distribution between and within countries and its changing epidemiology.

Recent radiographic surveys from Britain, New Zealand and continental Europe all indicate that there has been a dramatic decline (~50%) in Paget's disease over the past 30 years. This has been paralleled by a substantial decline in the clinical severity of the disease. Data from our centre indicate that, compared to 30 years ago, patients presenting with Paget's disease have substantially less extensive disease (median skeletal involvement 6% vs. 15%, $p<0.005$). The mean age of newly presenting patients has risen by 4 years per decade over the same time ($p<0.0001$). The most plausible explanation is that we are identifying the tail-end of severity in an ageing cohort, and that there are few incident cases. Such rapid change points strongly to the existence of a significant environmental factor in the pathogenesis of Paget's disease, to which exposure has substantially reduced. The accelerated urbanization of the past sixty years, and epidemiologic data linking Paget's disease to proximity to animals suggests that the agent could be a zoonosis. However, this hypothesis will be difficult to test empirically.

The strong epidemiological link with populations of British descent, and the marked familial clustering of Paget's disease prompted the search for disease-associated genes. The most robust link determined so far has been with the SQSTM1 gene, and more than 20 mutations in the ubiquitin-binding domain have now been associated with Paget's disease. To test the environmental hypothesis we have examined the development of Pagets' disease in adult offspring inheriting SQSTM1 mutations from affected parents. Our preliminary data indicate that if the offspring develop Paget's disease it is significantly later (~10 years, $p<0.0005$) than their parents, and with substantially less skeletal involvement - suggesting SQSTM1 mutations are permissive, but not causative, in the pathogenesis of Paget's disease.

S36
GENETIC BASIS OF PAGETS DISEASE

Stuart Ralston, *University of Edinburgh, /UK*

Paget's disease of bone (PDB) is a common condition characterized by focal abnormalities of increased bone turnover. Several other syndromes have been described which show clinical, radiographic and histological similarities to PDB and these, like classical PDB have a strong genetic component. Genome wide searches in PDB and related disorders have identified several susceptibility loci for the conditions and mutations have been identified in four genes that predispose to PDB and related disorders. The rare PDB-like syndromes of familial expansile osteolysis, early onset familial PDB and expansile skeletal hyperplasia are due to insertion mutations in exon 1 of the TNFRSF11A gene, which encodes receptor activator of NFkB (RANK), a critical regulator of osteoclast function. Inactivating mutations in the TNFRSF11B gene, which encodes osteoprotegerin, a decoy receptor for RANK, cause idiopathic hyperphosphatasia and TNFRSF11B polymorphisms appear to increase the risk for classical PDB. Mutations of the SQSTM1 gene, which encodes an important scaffold protein in the NFkB pathway, are the most important cause of classical PDB. So far, all disease causing mutations in this gene affect the ubiquitin associated (UBA) domain of the gene product and have been shown to cause loss of ubiquitin binding. Some workers have reported evidence to suggest that these PDB-causing mutations of SQSTM1 cause NFkB activation in vitro, but this has not been observed in all studies and the mechanisms by which UBA domain mutations of SQSTM1 regulate bone cell function are still poorly understood. The rare syndrome of hereditary inclusion body myopathy, PDB and frontotemporal dementia (IBMPFD) is caused by mutations in the VCP gene. This encodes valosin containing protein which amongst many functions has a role in targeting IkB for degradation by the proteasome. As in the case of SQSTM1, disease causing mutation affect a domain of VCP involved in ubiquitin binding. Several additional genes for PDB remain to be discovered, and strong candidate loci for the disease have been identified on Chromosome 5q31 and 10p13. It seems likely that other PDB-causing genes may also involve the RANK signaling pathway or the proteasomal processing of pathway components.

S37
INCLUSION BODY MYOPATHY ASSOCIATED WITH PAGET DISEASE OF BONE AND/OR FRONTOTEMPORAL DEMENTIA

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Mutations in p97/VCP cause inclusion body myopathy (IBM) with Paget's disease (PDB) and frontotemporal dementia (FTD)(IBMPFD). VCP is an AAA-ATPase gene associated with a variety of cellular activities, including cell cycle control, membrane fusion and in particular the ubiquitin (Ub)-proteasome mediated Endoplasmic Reticulum-Associated Degradation (ERAD) pathway. Most of the mutated residues are located in the ubiquitin binding domain. They are adjacent and potentially interact with each other (p.Arg155-p.Asn387, p.Arg159-p.Ala232 and p.Arg191-p.Leu198), suggesting that these residues may have a similar and specific function within the VCP homohexamer. Interestingly a mutation hotspot (P392L) close to the Ub-associated domain (UBA) of p62 in familial and sporadic PDB lends further support to the implication of this mechanism.

Mean age at diagnosis for myopathy and PDB is 42 years (range: 31-61 years) and for FTD, 55 years. IBMPFD is characterized by adult-onset proximal and distal muscle weakness (clinically resembling a limb-girdle muscular dystrophy), cardiac failure and cardiomyopathy being observed in later stages. Systematic immunohistochemical examination of IBMPFD patient muscle biopsies (4 families; 2 different mutations) revealed that 7/9 contained rimmed vacuoles while all had evidence of ubiquitinated and p97/VCP inclusions that were predominantly myonuclear, sarcoplasmic and subsarcolemmal in location.

Early stages of FTD are characterized by dysnomia, dyscalculia, comprehension deficits, paraphasic errors, and relative preservation of memory, and later stages by inability to speak, auditory comprehension deficits for even one-step commands, alexia, and agraphia. A systematic analysis of the neuropathologic changes in eight persons with IBMPFD and VCP mutations revealed Ub-positive neuronal intranuclear inclusions, dystrophic neuritis, and rare intracytoplasmic inclusions. The Ub pathology was abundant in the neocortex, less robust in limbic and subcortical nuclei, and absent in the dentate gyrus. Only rare inclusions were detected with antibodies to VCP. Analysis of the database of 231 members of 15 families for modifier genes suggests a potential link between APOE e4 genotype and the incidence of frontotemporal dementia.

PDB typically involves the spine, hips, scapulae and skull in 51% of affected individuals. PDB was frequently diagnosed because of elevated alkaline phosphatase. The mean value of total alkaline phosphatase in affected individuals was 389 U/L, with a range of 76-1724 U/L (normal range 30-130 U/L). Additionally, urine pyridinoline cross-link studies were elevated in all individuals affected by Paget disease and/or inclusion body myopathy and also gene carriers. Electron microscopy of PDB osteoclasts in 4 affected individuals from family 11 identified characteristic nuclear and cytoplasmic paired helical filaments (PHF) inclusions. The nuclear inclusions consisted of straight tubular structures of ~15 nm diameter also typically seen in sporadic cases of PDB. The nuclear and cytoplasmic inclusions seen in muscle were structurally very similar. Clinical, radiologic, biochemical, and mutation data analyzed in 103 individuals from 14 families indicated that individuals with the p.Arg155Cys mutation had an earlier age of onset of IBM ($p=0.01$) and those with the p.Arg155His mutation had a later onset of PDB ($p<0.05$) compared to the others.

The phenotype has been expanded based on findings in affected individuals from 27 families from North and South America and Europe harboring VCP missense mutations. Current laboratory studies of cell models and models of knockin / conditional knockout mice seek to characterize the molecular pathogenesis of VCP associated IBMPFD.

S39
LESSONS FROM THE PRISM TRIAL

Anne Langston, *Edinburgh, UK*

Paget's disease of bone is often treated by the use of bisphosphonates but it was previously unclear whether intensive therapy confers an advantage over symptomatic treatment in preventing complications or improving quality of life. The PRISM trial compared symptomatic treatment and intensive bisphosphonate therapy of 1324 Paget's disease patients, who were followed for a median of 36 months. The study used a randomised controlled trial methodology to reduce the influence of external factors, and the two treatment groups were balanced for key clinical and demographic criteria. The symptomatic group were treated only if they had Pagetic bone pain, for which they were given analgesics or anti-inflammatory drugs; this was followed by bisphosphonates only if they did not respond. The intensive group received repeat courses of aminobisphosphonates, irrespective of symptoms, with the aim of normalising serum total alkaline phosphatase. Several outcomes were measured including fracture rate, quality of life, progression of deafness and the requirement for joint replacement.

Related sub-studies used the same patient cohort to study health-related quality of life issues looking for predictors of reduced quality of life, and whether different personal reference frames affect a patient's health-related quality of life. Sub-studies investigating hearing loss in patients with skull involvement, blood loss associated with orthopaedic surgery, and the role of genetics and environmental issues

in the development of Paget's disease have also been carried out.

Results from the PRISM trial show that, in patients with established Paget's disease, there is no evidence to suggest that intensive bisphosphonate therapy is advantageous. Significantly better suppression of alkaline phosphatase occurred in the intensive therapy group ($p<0.001$). However, no differences could be seen in the occurrence of fractures, requirement of orthopaedic surgery, or hearing loss.

In addition, quality of life is not affected by biochemical control of the disease. However, some predictors of quality of life have been identified and it has been clearly demonstrated that Paget's disease patients have a reduced quality of life compared to the general population - mainly associated with reduced physical function. The use of disability aids can improve the functional mobility of Paget's disease patients.

S40

EXPERIMENTAL STUDIES IN PAGET'S DISEASE

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Paget's disease (PD) is one of the most exaggerated examples of abnormal bone remodeling with the primary cellular abnormality in the osteoclasts (OCL). In contrast to normal OCL, pagetic OCL are hyper-multinucleated and can form at very low concentrations of RANK ligand (RANKL), TNF-±, and 1,25(OH)2D3 and have increased expression of the TAF-II17 transcription factor. Both environmental and genetic factors appear to contribute to the pathophysiology of PD. Mutations in the p62 (sequestosome-1) gene occur in about a third of the patients with familial PD and in a minority of patients with sporadic PD, with the P392L amino acid substitution being the most common mutation observed. In addition, measles virus nucleocapsid transcripts and nucleocapsid protein (MVNP) have been detected in OCLs from patients with PD, although this remains controversial. Transfection of normal precursors with MVNP induces pagetic-like OCLs. Further, targeting the MVNP gene to cells in the OCL lineage in transgenic mice results in OCLs that share many characteristics of pagetic OCLs and the development of bone lesions, which are similar to those in Paget's patients. In contrast, targeting the mutant p62P392L gene to OCL in mice results in OCL precursors that do not express TAF-II17 or contain increased nuclei per OCL but are hyper-responsive to RANKL and TNF-±, but not to 1,25(OH)2D3. In addition, these mice develop progressive bone loss, but not the increased osteoblast numbers seen in PD. Recently, we have "knocked-in" the mutant p62P392L gene in mice, to determine its role in the bone microenvironment in PD. OCL precursors from "knock-in" mice were not hyper-responsive to 1,25(OH)2D3 nor expressed TAF-II17, but interestingly, marrow stromal cells from these mice produced increased amounts of RANKL in response to low concentrations of 1,25(OH)2D3. Histologic and histomorphometric studies of bones from these mice are currently underway and will be presented at the meeting. These studies suggest that both environmental and genetic factors are required for increased OCL activity and bone formation seen in patients with PD.

S41

GENE EXPRESSION IN CULTURED OSTEOBLASTS AND BONE MARROW STROMAL CELLS FROM PATIENTS WITH PAGETS DISEASE OF BONE

Ian R Reid, *Jillian Cornish, Dorit Naot. University of Auckland, New Zealand*

Paget's disease is a focal condition of bone of unknown cause. We have assessed gene expression by real-time PCR in primary cultures of osteoblasts and bone marrow stromal cells from pagetic patients and control subjects, to further investigate the pathogenesis of this condition. Candidate genes were identified based on known bone cell regulators, supplemented with microarray analysis. Dickkopf1 mRNA and protein levels were increased in both pagetic osteoblast and stromal cell cultures, and interleukins -1 and -6 were over-expressed in pagetic osteoblasts. These changes parallel recent findings in myeloma bone disease, with which there are some clinical similarities. Alkaline phosphatase was over-expressed and bone sialoprotein and osteocalcin were under-expressed in pagetic osteoblasts, consistent with their circulating levels in pagetic patients. It is hypothesized that over-expression of Dickkopf1, interleukin-1 and interleukin-6 could result in stimulation of osteoclast proliferation and inhibition of osteoblast growth, leading to the development of the characteristic lytic bone lesions. By stimulating osteoblast differentiation, Dickkopf1 and interleukin-6 may also promote mineralization, leading to the conversion of lytic lesions to sclerotic. These findings suggest that dysregulated gene expression of pagetic osteoblasts could cause the changes in bone cell number and function characteristic of Paget's disease.

Recent work has suggested that somatic mutations of SQSTM1 are common in the affected skeletal tissue of patients with Paget's disease. Therefore, we have re-examined this question using RNA collected from primary osteoblast and bone marrow cell cultures of patients with this condition. SQSTM1 was sequenced in cDNA samples from 14 osteoblast cultures, and from 15 cultures of bone marrow cells (8 collected at the time of surgery and 7 taken as needle aspirates from affected iliac crests). In these 29 samples drawn from 23 patients, the wild-type sequence of SQSTM1 was found in all but one marrow sample, which was heterozygous for the P392L mutation. DNA from peripheral blood in this subject had an identical sequence of SQSTM1, indicating that this

was a germ-line mutation. We conclude that somatic mutations for SQSTM1 are not commonly present in Paget's disease.

Finally, we have used these RNA collections to look for evidence of measles virus, in collaboration with Dr Muhammad Afzal. Expression of neither the measles virus nucleocapsid nor matrix genes were detectable in these samples.

We conclude that altered gene expression in bone cells is found in Paget's disease, but that this is not commonly associated with SQSTM1 mutations nor with the presence of measles virus.

S42

ZOLEDRONIC ACID IN THE TREATMENT OF PAGET'S DISEASE

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Modifications to the basic bisphosphonate structure have resulted in an increased ability to control osteoclastic bone resorption with a sustained effect over time. Zoledronic acid (ZOL) is the latest bisphosphonate to be introduced for the treatment of metabolic bone disease and illustrates the advantages of this process of drug evolution. Since Paget's disease is characterised by a substantial increase in bone turnover it is well suited for the study of a new bisphosphonate.

Increased potency means that abnormal bone turnover can be controlled with small doses of bisphosphonate given intravenously. A single 5mg ZOL infusion over 15 minutes will rapidly inhibit bone turnover resulting in disease control more quickly than that achieved by oral bisphosphonate spread over several weeks. This may be a clinical advantage in neurological vascular steal syndromes or where pain is severe. The degree of control of bone turnover is also better with 89% of patients achieving normal levels of serum alkaline phosphatase compared to 58% of those given oral risedronate.

Prolonged retention of ZOL within the skeleton results in more sustained disease control which in part is due to the lower post-treatment bone turnover. However matching for this characteristic, particularly at higher activities, shows that ZOL has additional effects which seem independent of previous therapy or pre-treatment bone turnover. Treatment with ZOL also led to an improvement in quality of life including physical function and bodily pain. The drug was well tolerated without evidence of renal impairment or symptomatic hypocalcaemia providing that patients were calcium and vitamin D replete. Post dose symptoms were more common with ZOL than risedronate but were mild and short lived.

These responses are a real advance and it is important to review current strategy to ensure that the full potential of this treatment is achieved. It remains to be seen whether long term control of Paget's disease reduces the development of late complications and whether problems such as bisphosphonate resistance can be avoided.

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P1

CIRCULATING CATHEPSIN K LEVELS BEFORE AND AFTER INTRAVENOUS BISPHOSPHONATE TREATMENT IN PAGET'S DISEASE OF BONE

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Paget's disease of bone (PDB) is a focal disorder of bone remodelling characterized by increased osteoclast-mediated bone resorption. Cathepsin K (CK) is actually the most abundantly synthesized protein of the active, resorbing osteoclast, and plays an important role in the degradation of the organic matrix of bone. This protease cleaves helicoidal and telopeptide regions of collagen type I, the major type of collagen in bone. The aim of the present study was to evaluate serum CK levels in 80 patients affected with PDB before and after treatment with intravenous bisphosphonates. Age and sex-matched subjects (n=55) not affected with PDB were also evaluated as control group. Circulating CK levels were determined by a specific sandwich enzyme immunoassay (Cathepsin K ELISA BI-20432, Biomedica, Austria). The detection limit was 1.1 pmol/l, and the intra and inter-assay coefficients of variation were 4% and 6% respectively. Serum total alkaline phosphatase (ALP), carboxyterminal cross-linked telopeptide of type I collagen (sCTX) and bone-specific ALP (BALP) were also measured for comparison. Pre-treatment CK levels were significantly higher in PDB patients than in males and females controls (11.13±4.7 vs. 3.7±1.9, $p<0.05$), as well as in polyostotic vs. monostotic PDB. Moreover, in untreated PDB subjects baseline CK positively correlated with sCTX ($r=0.57$, $p<0.001$), ALP ($r=0.34$; $p<0.01$) and BALP ($r=0.35$; $p<0.01$) levels. After recruitment, 53 of the 80 PDB patients were treated with pamidronate (30 mg i.v. for 2 days, n=32) or zoledronate (4 mg i.v. single infusion, n=21) and follow-up serum sampling was performed at 3, 30, 90, 180 and 360 days. Overall, bisphosphonate treatment significantly reduced CK levels between 3 and 90 days. The nadir occurred earlier in CK than sCTX, ALP, or BALP levels. Thereafter an increase in CK was observed. The reduction in CK at each time point was significantly higher in patients treated with zoledronic acid than in those treated with pamidronate. Importantly, the early decrease in CK levels was significantly higher in responders than non responder patients to pamidronate. These data suggest that serum CK measurements could be a valuable parameter in the evaluation of subjects with PDB as well as in the follow up of treatment.

P2

EFFICACY AND SAFETY OF ZOLEDRONIC ACID IN PAGETS DISEASE OF BONE: 4 YEARS OF EXPERIENCE

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Bisphosphonates, potent inhibitors of bone resorption, are nowadays the first-line therapy for Paget's disease of bone (PDB). Zoledronic acid (ZA), an aminobisphosphonate with potent antiresorptive activity in bone, which is currently the most potent of its class available and no detectable impairment of bone mineralization has been found. The aim of this study was to assess the safety and therapeutic efficacy of ZA in patient with active PDB who had become resistant to other antiresorptive therapies, as well as the safety and tolerability of the drug, during the follow-up for 48 months.

Each patient received a single 5 mg intravenous infusion of ZA over a 15-minute period. The following variables were taken: gender, age at the time of diagnosis, number of locations, bone scan distribution, and time of the disease evolution. And the biochemical markers of bone turnover were determined: serum total alkaline phosphatase (SAP) level , serum bone-specific alkaline phosphatase (bALP) and the ratio of urinary levels of the N-telopeptide of type I collagen to creatinine (NTx) at baseline and 6, 12, 18, 24, 30, 36, 42 and 48 months after infusion. Assess the proportion of patients who had a therapeutic response (defined as normalization of the alkaline phosphatase level) at six months and the evolution of the biochemical markers of bone turnover during the follow-up for 48 months and the safety of ZA. The statistical study was by means of SPSS for Windows (v12). 5 patients with PDB active were included (2 women/ 3 men), mean age at the time of diagnosis was 62.8 ± 10.73. A normalization of biochemical markers of disease activity was observed a total of patients, at the six months of follow-up, with the persistence of these effects during the four years of follow-up. As well clinical features and bone scintiscan normalization presented.

In this study, a single infusion of ZA provided a significantly greater therapeutic response and produced a more long-lasting biochemical and clinical remission in our patient with active PDB than others conventional antiresorptive therapies.

In conclusion, this study demonstrates the safety and efficacy of ZA in patients affected by active PDB.

P3
IS PLAIN ABDOMINAL X-RAY A SENSITIVE TOOL FOR THE SCREENING OF PAGET'S DISEASE OF BONE?

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According to our results, in a 19% of patients with Paget Disease of Bone (PDB) the diagnostic test that originally raised suspicions among medical staff was a plain abdominal x-ray (AXR) requested in order to study an abdominal complaint. Some authors have proposed this indicator as a tool for the screening of PDB in the general population.

Objective. To measure the diagnostic value of AXR for the diagnosis of PDB and to evaluate the clinical characteristics of patients with bone lesions in the AXR when compared with patients without.

Methods. Patients diagnosed of PDB with an AXR were selected from a series of 276 PDB patients. We analysed the clinical, laboratory and treatment data. We considered two groups: A (patients with bone lesions in the AXR) and B (patients without bone lesions in the AXR). The groups were tested for an association with different parameters. A second comparison was made between patients with or without PDB lesions in the abdominal area according to bone scan results. For the comparison of proportions, X2 was used and OR calculated. T-test was used for continuous variables.

Results. 163 patients were studied. 112 patients (68,7%) had bone lesions in AXR. In the 51 patients (31,3%) with normal AXR, the PDB bone lesions were located in; skull 30 (60%), distal femur 10 (20%), tibia 8 (16%), humerus 7 (14%) and shoulder blade 1 (2%). For the comparison of bone scan results, 235 cases were studied. 175 (74,5%) had bone lesions in the abdominal area. The difference in % of familial cases and the number of bones affected was higher in group A.

Conclusion. AXR is not a sensible tool for the diagnosis of PDB since one third of patients were not diagnosed with this test. There were no differences between patients with or without bone lesions in abdominal area except for the percentage of familial cases and the number of bone lesions.

P4
LONG-TERM EFFECTS OF SINGLE ZOLEDRONATE OR NERIDRONATE INFUSION IN PAGET'S DISEASE OF BONE

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Aminobisphosphonates actually represent the most common treatment for Paget's disease of bone (PDB), with the potential for sustained remission. Intravenous regimens with different compounds demonstrated improved efficacy and compliance with respect to oral regimens. However, there have been few head to head randomized trials comparing intravenous bisphosphonates, and it is not demonstrated if these drugs differ in therapeutic efficacy. We performed a randomized study comparing intravenous pamidronate to zoledronate or neridronate in 90 subjects with active PDB. We report the results from the trial and the post-trial follow up of patients. At baseline patients were randomly assigned to receive either a 4 mg infusion of zoledronic acid (n=30) or a 30 mg infusion of pamidronate for 2 consecutive days every 3 months (n=60). After 6 months non-responders to pamidronate were crossed over to zoledronate (n=18) or neridronate (n=15, infusion of 100 mg for 2 consecutive days) treatment. Blood samples were collected at baseline and after 1, 3, 6, 12, 15, 18, and 24 months. No bisphosphonate was given after the cross-over, during the extension study. At 6 months, normal ALP levels were achieved in 93% of patients in zoledronate group and in 35% of patients in pamidronate group. Normalization of ALP levels was maintained in 79% and 65% of patients in the zoledronic acid group, after 12 and 24 months follow-up, respectively, while loss of therapeutic response was observed in 2/30 (6%) at 24 months. Among non-responders patients to pamidronate, 14/15 (93%) in the neridronate group and 17/18 (94%) in the zoledronate group achieved a therapeutic response after 6 months from the cross-over. Similar normalization rates were also observed between neridronate (80%) and zoledronate (83%) treated subjects at 6 months. Moreover, at 18 months from cross-over treatment (corresponding to 24 months from the baseline visit) ALP normalization was maintained in 60% and 77% of patients in neridronate or zoledronate group, respectively. In conclusion, single neridronate and zoledronate infusion produced a rapid and sustained control of bone turnover in up to 90% of PDB patients non-responders to pamidronate. This effect was largely independent of pre-treatment disease activity and prior bisphosphonate therapy.

P5

MANAGEMENT OF PAGET'S DISEASE OF BONE: AN AUDIT OF CLINICAL PRACTICE IN AUSTRALIA

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Background and objectives. Consensus guidelines for the treatment of Paget's disease of bone have been published, but is not known how closely these reflect clinical practice. The aim of this study was to examine the treatment of Paget's disease of bone by specialist physicians in Australia.

Methods. We conducted a multi-centre, stratified retrospective audit of the medical records of 531 subjects treated for Paget's disease of bone between 2000 and 2005 in 29 Australian centres, and circulated a questionnaire to 34 participating specialists regarding their usual clinical practice.

Results. The 531 subjects comprised 287 males and 244 females aged 41 to 97 years. The most recent treatment was oral bisphosphonate therapy in 57% of subjects (alendronate 29%, risedronate 24%, tiludronate 4%) and intravenous therapy in 43% (pamidronate 33%, zoledronic acid 10%). Intravenous therapy was more commonly used in hospital settings (65%) than in community-based private practice (35%). Symptoms and increased alkaline phosphatase activity were the most common criteria for initiating treatment, accounting jointly for over 80% of treatment courses. Intolerance to oral therapy was the highest ranked criterion for deciding between intravenous or oral therapy. Approximately 80% of oral therapy courses were at the recommended dose and frequency. There was greater variability in intravenous treatment regimens, with pamidronate infusions most commonly administered at three monthly or annual intervals.

Conclusions. Oral and intravenous bisphosphonate therapy are both commonly used to treat Paget's disease of bone in Australia. There is a lack of consensus as to the optimal regimen for intravenous pamidronate treatment.

P6

RAPID PAIN RELIEF AND CLINICAL IMPROVEMENT WITH INTRAVENOUS ZOLEDRONIC ACID IN LOCALIZED TRANSIENT OSTEOPOROSIS OF THE HIP

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Localized transient osteoporosis (LTO; bone marrow edema) is an increasingly diagnosed condition characterized by acute onset of disabling bone pain, which typically occurs at a single skeletal site. Although its etiology is unknown, LTO has been linked to pregnancy and prolonged periods of exercise but there is no previous trauma or surgery as in algodystrophy. Current treatment options are limited in number and provide inadequate efficacy except recent positive experience with intravenous bisphosphonates.

Zoledonic acid, a very potent, nitrogen-containing bisphosphonate, has been used worldwide in metastatic bone disease and more recently in benign skeletal disorders such as Paget's disease (1) and osteoporosis (2). We enrolled 8 patients with LTO of the hip into a 6-months, open label, observational study to investigate the therapeutic efficacy of one infusion of 5mg zoledronic acid. Additionally all patients received a daily supplementation with 1200 mg calcium and 800 IU vitamin D. Diagnosis was based in all cases on typical history, bone marrow edema in MRI, bone scan and conventional x-ray. Local pain at the affected hip was measured at onset and after 2 weeks, 1, 3 and 6 months using a visual analogue scale (VAS 1-10). Furthermore walking disability and impairment in quality of life was documented during follow up. BMD at the lumbar spine and both total hip area was measured at baseline and 6 months thereafter.

Three men and five women who had a pain duration between 1 and 8 months and a mean age of 53 years (range: 35-63) participated in the therapeutic trial. Affected were the left hip in 5 and the right in 3 patients. In no patient a previous trauma could be documented but 7 of 8 patients had the following concomitant diagnoses: pregnancy 2, osteopenia 2, osteogenesis imperfecta 1, corticoid-induced osteoporosis 1, idiopathic osteoporosis 1. The mean baseline BMD T-score at the lumbar spine was 1.9, at the involved hip - 2.0 and at the unaffected hip - 1.4.

At 6 months after the BP-infusion VAS pain score had decreased from 9.4 (at baseline) to 0.4 The robust effect on pain after the administration of zoledronic acid was rapid in almost all patients as visualised by individual VAS pain scores. Only in one patient we decided to give a second infusion after 3 months. In parallel there were significant improvements in mobility and QoL. Relative to baseline, mean lumbar spine BMD increased by 4.1%

after 6 months of treatment and at the affected and unaffected hip by 9.4% and 3.0% respectively (difference 6.4%, p < 0.01). We conclude that an infusion of 5 mg zoledronic acid is highly effective in reducing pain, restoring BMD at the affected area and improving mobility and QoL in patients with localized transient osteoporosis of the hip.

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P7

TREATMENT OF HUNGARIAN PATIENTS WITH PAGET'S DISEASE OF BONE WITH ZOLEDRONIC ACID

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Paget's disease of bone (PD) is a chronic skeletal disease characterized by an excessive resorption, or breakdown, of bone and subsequent abnormal formation of bone tissue that, over time, causes affected bones to weaken. Zoledronic acid, a new generation of bisphosphonate was shown to inhibite bone resorption after a single 4 mg intravenous infusion.

The aim of this study was to show the effect of a single 5 mg infusion of zoledronic acid on serum alkaline phosphatase (AP), a marker of disease activity in patients with PD. The gene expression pattern of pagetic monocytes was also to be determined.

Blood tests were performed to measure levels of the enzyme alkaline phosphatase in 18 patients (8 males and 10 females) with PD (12 monostotic and 6 polyostotic), aged 42-89 years. Peripheral blood monocytes were separeted from 6 patients before and 3 month after zoledronic acid infusion. Visual analog scale (VAS) were performed before and 3 months after infusion.

At 3 months after zoledronic acid infusion alkaline phosphatase levels were normalized in 9 cases out of 13 patients (69%) and resulted in improvements measured on VAS scale in 17 cases out of 18 patients (94%). No significant change from baseline was noted in either serum calcium or creatinine at 3 months. The most frequent side effect was a flu-like syndrome, observed at 8 patiens. The IFN-alpha (3,6 ± 0,27), IFN-betha (2,61 ± 0,17) and IFN-gamma (1,91 ± 0,28) genes were significantly up-regulated in untreated pagetic monocytes as compared to the healthy controls. This initial up-regulation of the IFN (alpha ,betha, and gamma) genes were normalized 3 months after iv zolendronate therapy in 6 PD patients.

In conclusion, single 5 mg infusion of zoledronic acid is a safe and effective treatment for patients with both mono and polyostotic Paget's disease of bone. Gene expression profile analysis revealed that interferon genes may play a role both in the pathogenesis and in the mechanism of action of zoledronic acid in Paget's disease.

P8

A NOVEL MUTATION (P364S) UPSTREAM OF THE UBA DOMAIN IN SEQUESTOSOME 1/P62 ASSOCIATED WITH PAGET'S DISEASE WITH A MILD PHENOTYPE

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Background. Mutations in the sequestosome 1/ p62 (p62) gene are associated with Paget's disease of bone (PDB) linked to the 5q35 locus. Mutations described to date cluster within the C-terminal ubiquitin-associated (UBA) domain of p62, and patients with truncating mutations of p62 in or close to the UBA domain generally suffer more severe disease than those with missense mutations. We investigated our cohort of familial PDB patients for p62 mutations.

Methods. Patient DNA was screened for p62 mutations in exons 7 and 8. After PCR amplification, exon 8 DNA was examined for the presence of the P392L mutation, commonly associated with PDB, by SacII digestion. Amplicons of exons 7 and 8 were routinely sequenced using the Big Dye Terminator Verion 3.1 ready reaction sequencing kit.

Results. In a patient with PDB, we identified a novel heterozygous mutation in exon 7, a C to T transition at position +1090, resulting in a serine for proline substitution at codon 364 (P364S). Evident in both forward and reverse sequencing chromatograms, the mutation was confirmed by HaeIII digestion, since the presence of the mutation abolishes a HaeIII site in the affected allele. Examination of a series of normal chromosomes failed to detect the mutation, providing evidence against a polymorphic change. The mutation occurs within the PEST sequence immediately upstream of the p62 UBA domain. The patient has a mild phenotype, with PDB diagnosed at 54 years of age affecting skull, L5 vertebra and sacrum and plasma alkaline phosphatase 160 U/liter (< 135).

Conclusion. A novel mutation, P364S, located upstream of the p62 UBA domain, is associated with PDB with a mild phenotype. Functional studies are under way to examine the effect of this mutation on p62 and osteoclast function.

P9

DISEASE-ASSOCIATED MUTATIONS IN THE SIGNAL PEPTIDE OF RANK ALTER RANK LOCALISATION AND DOWNSTREAM ACTIVATION OF NFKB

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RANK is a transmembrane receptor required for osteoclast formation. Insertion mutations have previously been identified in the signal peptide of RANK in patients with familial expansile osteolysis (FEO), severe/early onset Paget's Disease (PDB) and Expansile Skeletal Hyperphosphatasia (ESH). It has been suggested that these mutations cause overactivation of NFkB, thereby stimulating osteoclast formation. To examine this further, FLAG-tagged wildtype and mutant RANK cDNA constructs were overexpressed by transient transfection in HEK293 cells. Wildtype (WT-) RANK was localised by immunofluorescence to the plasma membrane and the golgi, whereas FEO-, PDB- and ESH-RANK were not detected at the plasma membrane and appeared to accumulate in the endoplasmic reticulum (ER) and in punctate, cytoplasmic structures. Immuno-TEM analysis identified these structures as multilamellar extensions of the ER. Furthermore, ultrastructural studies showed that all three mutant forms of RANK, but not WT-RANK, induced areas of intermediate filaments in transfected 293 cells, a feature commonly associated with overexpression of misfolded proteins and with inhibition, or overload, of the proteasome. In 293 cells, transient expression of mutant and WT-RANK constructs caused similar levels of constitutive activation of NFkB, but only WT-RANK-transfected cells showed further activation upon treatment with RANKL, consistent with the lack of functional RANK at the plasma membrane in cells expressing RANK with the FEO, PDB or ESH mutations.

By contrast to overexpression, in cells stably expressing single copies of WT-, FEO-, PDB- or ESH-RANK there was no constitutive activation of NFkB. When the cells were stimulated for 60 minutes with RANKL, only cells stably expressing WT-RANK showed an increase in NFkB activation above that of the parental 293 cell line, consistent with localisation of WT-RANK (but not the mutant forms) to the plasma membrane.

These results show that the FEO-, PDB- and ESH-mutations prevent the correct processing and delivery of functional RANK protein to the plasma membrane, preventing RANK ligand-dependent activation of NFkB. The mutant forms of RANK do not appear to cause constitutive activation of NFkB except (like WT-RANK) when artificially overexpressed. The exact manner in which these mutations stimulate osteoclast formation/survival in FEO, PDB and ESH therefore remains to be determined.

P10

EFFECT OF SQSTM1 MUTATIONS ON BONE CELLS IN VITRO

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A number of mutations in the gene encoding Sequestosome-1(SQSTM1)/p62 have been identified in patients affected with Paget's disease of bone (PDB). PDB is characterised by focal increases in both osteoclastic resorption and bone deposition by osteoblasts. Previous studies in overexpression and stable cell line systems have shown that expression of SQSTM1 mutations (P392L and truncating mutants) result in osteoclasts that are larger, contain more nuclei and have greater resorptive capacity, mimicking the cellular phenotype observed in patients with PDB. In this study, we have examined the effects of three SQSTM1 mutations - P392L, E396X and G425R - on osteoclast formation in suboptimal conditions, and on osteoblast growth and function.

To examine osteoclast formation, M-CSF-dependent human peripheral blood monocytes were treated for 24 hours with 100ng/ml RANKL. Cells were trypsinised, electroporated with SQSTM1 constructs (Amaxa), seeded into 96-well plates in quadruplicate and cultured in the presence of M-CSF only for a further six days. Cells were then fixed and stained for VNR and nuclei. For each well, cells positive for VNR with three or more nuclei were counted. For osteoblast growth studies, cultured mouse calvarial osteoblasts were trypsinised and electroporated with SQSTM1 constructs. Following electroporation, cells were cultured for a further 48 hours and then assayed for growth and alkaline phosphatase activity.

Following 24 hours pre-treatment with RANKL, all mutations resulted in increased osteoclast-like cell formation compared with either empty vector or wild-type control in the presence of M-CSF only. This increase was significant for both the E396X ($p=0.002$) and G425R ($p<0.001$) mutants. In mouse calvarial osteoblasts, expression of SQSTM1 mutants did not have significant effects on alkaline phosphatase activity. However, growth was significantly affected ($p=0.007$). For both P392L and E396X, osteoblast growth was retarded compared with wildtype; for G425R, osteoblast growth was increased.

These preliminary results suggest that SQSTM1 mutations affect cells of both the osteoclast and osteoblast lineage. In osteoclasts, the mutations may act in a permissive manner to promote osteoclast formation. In osteoblasts, the effect of the mutations on growth varies between mutations, suggesting that different mutations may act by different mechanisms.

P11

EFFECTS OF PAGET'S DISEASE OF BONE MUTATIONS ON THE UBIQUITIN-BINDING FUNCTION OF SQSTM1

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Mutations affecting the SQSTM1 signalling adapter protein are commonly found in patients with Paget's disease of bone (PDB). We have extended our previous in vitro functional analyses of PDB-mutant SQSTM1 proteins [Cavey et al. (2006) Calcif. Tissue Int., 78:271-7] to study the effects of other PDB mutations on the ubiquitin-binding properties of SQSTM1. These include mutations which affect regions of SQSTM1 outside of the ubiquitin-binding UBA domain (A381V, and a mutant equivalent to a predicted product of the G1205C splice-site mutation which lacks amino acids 351-388 [Beyens et al. (2006) Calcif Tissue Int., 79:281-8]), as well as a double mutation involving the P392L and S399P changes on the same allele [Eekhoff et al. (2004) Arthritis Rheum., 50:1650-4]. In accordance with our previous findings, both of the non-UBA domain mutations showed deleterious effects on ubiquitin-binding by SQSTM1, further emphasising the important role of non-UBA domain sequences in mediating ubiquitin-recognition, as well as in PDB aetiology. The P392L/S399P double mutant showed a more severe effect on ubiquitin-binding than either of the single P392L or S399P missense mutations alone. As this double mutation was associated with a particularly severe phenotype, our findings are supportive of the proposal that disease severity in PDB with SQSTM1 mutations may be directly related to the effects of the mutations on the ubiquitin-binding function of the SQSTM1 protein.

P12

EVIDENCE OF ELEVATED ALP LEVELS IN CLINICALLY UNAFFECTED RELATIVES OF SUBJECTS WITH ªFAMILIAL PAGET'S DISEASE OF BONE

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Paget's disease of bone (PDB) is a focal disorder of bone remodelling. Clinical signs and symptoms vary widely depending to the number and location of affected skeletal sites. The disease is often asymptomatic and diagnosis is generally based on increased markers of bone turnover associated with typical bone scan and radiological signs. Importantly, genetic factors have been increasingly associated with PDB, even though the molecular basis still remains unclear. We recently performed a detailed screening of family members of familial PDB cases (n=39) in a cohort of 194 PDB subjects. All first degree and second degree relatives were contacted and 139 of them accepted to be investigated for the presence of PDB. Those having serum total or bone specific alkaline phosphatase (ALP) levels above the normal limits (and/or other suspected features of PDB) were invited to undergo a bone scan, followed by x-ray examination of areas of increased isotope uptake.

We identified 5 new cases of PDB in the 139 investigated relatives. Pedigree analysis confirmed an autosomal dominant pattern of inheritance, with the disease being transmitted through both paternal and maternal sides. Interestingly, we also identified 3 young subjects (32-44 yrs old) with elevated total and bone ALP levels but without any other clinical sign or symptom characteristic of PDB. In particular, the Tc 99m bone scan did not evidence any skeletal alteration or increase in isotope uptake and X-ray examination of the spine, skull, femurs and tibiae confirmed the absence of pagetic localizations. A further biochemical screening in these subjects confirmed elevated total and bone ALP levels as well as increased levels of cathepsin k and carboxyterminal cross-linked telopeptide of type I collagen. A further subject (32 yrs old), with normal total ALP levels referred a traumatic fracture at L3 vertebra. A subsequent Tc99m bone scan disclosed a single marked increase of isotope uptake in L3 and the X-ray of the spine showed the presence of a suspected pagetic localization in L3. The patient underwent a bone biopsy that confirmed a histological pattern of PDB. For all these subjects a genetic screening for SQSTM1 mutation is actually in progress.

P13

IDENTIFICATION OF GENDER-SPECIFIC ASSOCIATION BETWEEN TNFRSF11B POLYMORPHISMS AND PAGET'S DISEASE OF BONE

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Although Juvenile Paget's disease has been shown to be caused by mutations in TNFRSF11B encoding osteoprotegerin, mutations in this gene have never been found in typical Paget's disease of bone (PDB) patients. However, there are indications that polymorphisms in TNFRSF11B might contribute to the risk of developing PDB.

In order to investigate this further, we recruited a population of 131 Belgian patients with sporadic PDB and 171 Belgian controls. By means of the HapMap we selected 17 SNPs that, in combination with 4 multi-marker tests, contain most information on common genetic variation in TNFRSF11B. In order to replicate the findings observed in the Belgian study population, genotyping data of SNPs generated in a UK population were reanalyzed.

In our Belgian study population, associations were found for 2 SNPs (rs11573869, rs1485286) and for one multi-marker test involving rs1032129. When subsequently analyzing males and females separately, these associations turned out to be driven by females (56 cases, 78 controls). In addition, 3 other tagSNPs turned out to be associated in females only. These were: rs2073617 (C950T), rs6415470 and rs11573869. Reanalysis of genotyping data from a UK study population indicated that the associations found for C950T and C1181G were also exclusively driven by females (146 cases, 216 controls). Meta-analysis provided evidence for risk increasing effects of the T allele of C950T and the G allele of C1181G in the female population (p-values 0.002 and 0.003 respectively). The haplotypes formed by the SNPs associated in the Belgian population were also distributed differentially between female cases and controls.

In conclusion, we have shown for the first time that SNPs influencing the risk to develop Paget's disease of bone could be sex-specific. Further research is necessary to identify the causative variants in TNFRSF11B and to elucidate the molecular pathogenic mechanism.

P14

MICE WITH A TRUNCATION MUTATION AFFECTING SQSTM1 EXHIBIT SEVERAL PHENOTYPIC FEATURES IN COMMON WITH PAGET'S DISEASE OF BONE

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Background: Paget's disease of bone (PDB) is characterized by focal increases in bone turnover and mutations affecting the Sequestosome 1 gene (SQSTM1) are an important cause of this condition, occuring in up to 40% of patients with familial PDB.

Methods: Here we report upon our preliminary analysis of the skeletal phenotype of mice with a truncating mutation at codon 409 of the SQSTM1 gene which deletes most of the UBA domain and results in loss of Ubiquitin binding.

Results: Radiological analysis has shown femoral expansion in mutant mice by a mean ± SD of 8.63 ± 4.31% when compared with wild type (WT) ($p<0.0001$). Preliminary histomorphometric analysis showed a dramatic increase in bone turnover in 20-month old mice that are homozygous carriers of the mutation. There was a 3-fold increase in osteoclast number from 1.2 ± 0.5 /mm2 in WT to 4.5 ± 0.8 / mm2 in mutant ($p<0.01$) and a two fold increase in eroded surface from 6.1 ± 2.0 % to 13.2 ± 1.8 % ($p<0.01$). Osteoblast numbers were also increased from 15.2 ± 4.0 / mm2 in WT to 37.5 ± 5.0 / mm2 in mutant ($p<0.01$). Studies in vitro showed a 8.6 ± 14.4% increase in RANKL-induced osteoclast formation in mutant mice compared with WT ($p=0.03$). There was no difference in osteoblast growth between genotypes, but alkaline phosphatase activity was significantly lower in mutant compared with WT osteoblasts (46.5 ± 16.9% reduction; $p<0.001$). Analysis using microCT in identified lytic lesions in the femur in 20 month old mutant mice whereas similar lesions have not yet been identified in WT. Histological analysis is currently in progress. Osteoarthritis of the knee was also more common in mutant mice; 9/16 (56%) vs. 4/12 (33%), but the difference was not significant.

Conclusions: We conclude that mice carrying a truncating mutation of the SQSTM1 gene exhibit several features that are reminiscent of PDB including increased bone turnover, lytic lesions, and osteoarthritis. Further studies are in progress to conduct more detailed characterisation of the skeletal phenotype and define the mechanisms by which this mutation regulates bone cell activity.

P15

MUTATION AND HAPLOTYPE ANALYSIS OF THE SQSTM1 GENE IN BELGIAN PAGET'S DISEASE OF BONE PATIENTS

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Until today, 14 different Paget's disease of bone (PDB)-causing mutations have been identified in SQSTM1, with the 1215C/T (P392L) mutation being a recurrent one. Recently, Lucas et al. reported that the P392L mutation occurred on a common genetic background in the majority of the British PDB patients, providing evidence for a founder effect (1). Here we investigated the frequency of SQSTM1 mutations and the haplotypes surrounding the P392L mutation in a sporadic Belgian PDB population.

Exon 7 and 8 of SQSTM1 were sequenced in 212 sporadic Belgian patients. To investigate the haplotypes surrounding the P392L mutation we genotyped 4 SNPs in exon 6 and the 3'UTR (rs4935C/T, rs4797G/A,

rs10277T/C and rs1065154G/T) in all P392L carriers and 28 Belgian controls. Haplotypes were estimated using W H A P (http://pngu.mgh.harvard.edu/~purcell/whap/).

We identified 15 patients with a mutation (7.1%). Fourteen patients were heterozygous for 1215C/T and one patient carried the IVS7+1G/A mutation. Construction of the haplotypes in 28 Belgian controls revealed that the H1 (TACT), H2 (CGTG), H3 (TGTG) and H4 (CATG) haplotypes had frequencies of 55.36%, 41.07%, 1.79% and 1.79% respectively. The frequencies of these 4 haplotypes in P392L cases were 32.14%, 60.71%, 3.57% and 3.57% respectively. Although at this moment we have not yet defined on which haplotype of the patients the 1215C/T substitution occurred, we observed that all P392L carriers have at least one H2 haplotype. Given that the frequency of the H2 haplotype in the control population is 0.411, the chance that within a group of 14 random individuals all of them would carry at least one H2 haplotype is 0.0026. This strongly supports the hypothesis that there could be a common ancestor mutation in all 14 patients.

The frequency of SQSTM1 mutations in our sporadic Belgian PDB population is somewhat lower than previously reported for other populations. Fourteen patients carry the 1215C/T mutation and haplotype analysis indicates that all of them carry at least one H2 haplotype. Further analysis will reveal whether the C to T transition occurred in all cases on this H2 haplotype supporting the idea of a founder mutation.

(1) Lucas et al. 2005 JBMR 20(2): 227-231.

P16

PREVALENCE OF SQSTM1 MUTATIONS IN SALAMANCA, SPAIN

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Paget's disease of the bone (PDB) is a common disease with a strong genetic component. It has been reported that mutations in the ubiquitin-associated (UBA) domain of the Sequestosome 1 (SQSTM1) gene are involved in PDB. Due to the marked geographical differences in the prevalence of PDB, we have studied the presence of SQSTM1 mutations in 47 families with PDB from Salamanca, a province in central-western Spain. We have amplified all exons by PCR as well as intron-exon boundaries of the SQSTM1 gene and the amplified fragments ranging in size from 200 to 500bp were screened for mutations with heteroduplex analysis. Since no muation was detected, we did not study the promoter or the 3' untranslated region (3'UTR). Our results show that in the families included in our study we did not find any mutation. We have previously reported that our population may be considered a cluster and these results suggest that PDB patients from our region could carry a mutation in a gene other than SQSTM1 that would predispose to PDB.

P17

SQSTM1 MUTATIONS AND PAGET'S DISEASE OF BONE - FUNCTIONAL AND STRUCTURAL STUDIES

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We recently proposed that UBA domain mutations of SQSTM1 predispose to PDB by a common mechanism which involves loss of ubiquitin-binding [Cavey et al. (2006) Calcif. Tissue Int., 78:271-7]. Preliminary studies suggest a relationship between the effects of different mutations on the ubiquitin-binding function of SQSTM1 and disease severity, supportive of a central role in disease aetiology. The effects on ubiquitin-binding of many of the PDB mutations of SQSTM1 can be explained by either reduced stability of the UBA domain and/or disruption of the ubiquitin-binding interface, however the mechanism by which several of the mutations affect ubiquitin-binding cannot be easily explained. New structural insights into the novel mechanism of ubiquitin-recognition by SQSTM1 may provide a rationalisation of how these mutations exert their effects, as well as clearer understanding of the normal physiological significance of ubiquitin-binding by SQSTM1.

P18

CANONICAL AND NON-CANONICAL MECHANISMS OF OSTEOCLAST FORMATION IN PAGET'S DISEASE OF BONE

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A balance between bone resorption and formation, carried out respectively by osteoclasts and osteoblasts, is essential for maintaining normal bone structure. A shift in this balance may result in increased bone loss, a key feature of Paget's disease. RANKL and M-CSF are two key growth factors required for osteoclast formation from circulating mononuclear phagocyte precursors. Recently, a number of cytokines/growth factors have been identified which can substitute for either RANKL or M-CSF to induce osteoclast formation. In this study we have determined whether LIGHT and HGF can substitute for RANKL and M-CSF respectively to induce osteoclast formation in Paget's disease patients. Peripheral blood mononuclear cells (PBMCs) were isolated and cultured for up to 21 days in M-CSF (25ng/ml) ± RANKL (30ng/ml) or LIGHT (50ng/ml) and with RANKL and HGF (25ng/ml). Large numbers of TRAP+/VNR+ multinucleated cells (MNCs), capable

of lacunar resorption, formed in both HGF and LIGHT-treated cultures. The number of TRAP+ MNCs that formed in LIGHT and HGF treated cultures was 62.4% and 36.3% respectively relative to the M-CSF/RANKL treated positive control; lacunar resorption was 92.1% and 4.1% respectively relative to the positive control. LIGHT-treated cultures produced a large number of small individual areas of resorption. Our findings indicate that both canonical (RANKL/M-CSF-dependent) and non-canonical (RANKL/M-CSF-independent) pathways can induce osteoclast formation in Paget's disease. Further investigation of the role of LIGHT and HGF, as well as other factors that activate RANKL/M-CSF independent pathways of osteoclast formation, are indicated to determine whether these factors play a role in the pathogenesis of Paget's disease.

P19

P62 SIGNALING IN OSTEOCLASTS AND SURVIVAL PATHWAYS

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In Paget's Disease of Bone (PDB), osteoclasts (Ocs) are increased in size and number, and Oc precursors are hypersensitive to osteoclastogenic signals (e.g. RANKL, 1,25-OH2-D3), suggesting a misregulated signaling. Numerous mutations reported to date in PDB cluster in the Ubiquitin Binding Associated (UBA) domain of the signaling protein p62, impairing its ability to bind ubiquitin chains, and potentially affect protein degradation or protein-protein interactions. As p62 is an important player in RANKL signaling, our aim was to study the interactions between p62 and proteins classically involved in cell survival. We first determined the effects of p62 mutations on apoptosis in human Ocs differentiated from cord blood monocytes. A full-length wild-type p62 (p62{super}wt{/super}), and p62 mutated genes (p62{super}P392L{/super}, p62{super}deltaUBA{/super}) were cloned in a pEGFP-C2 plasmid. Fully differentiated Ocs transfected with p62{super}P392L{/super} or p62{super}deltaUBA{/super} displayed massive cytoplasmic aggregates, contrary to Ocs transfected with p62{super}wt{/super} or empty vector. Basal apoptosis occurred in about 50% of Ocs transfected with an empty vector or p62{super}wt{/super}, and the rate of apoptosis was much lower in p62{super}deltaUBA{/super} or p62{super}P392L{/super} transfected Ocs. To better understand the cascade of events linked to p62 after RANKL stimulation, and their relation to Oc survival, we studied by immunofluorescence the localization of p62 and kinases involved in survival pathways: zetaPKC, closely linked to p62, p70S6 kinase and the Phosphoinositide Dependant kinase 1 (PDK1), whose roles in Oc signaling are currently unknown. PDK-1 is a critical kinase for Akt activation, but is also involved in the activation of zetaPKC and p70S6 kinases, and may act as a nucleo-cytoplasmic shuttling protein. RANKL stimulation induced a nuclear relocalization of p62 and its known partner zetaPKC, a similar relocalization of PDK-1 (hallmark of its activation), but no change in p70S6 kinase localization. This suggests that PDK-1 could be involved in the kinase activation associated with the p62 signaling complex and its localization to the nucleus. Taken together, our results suggest that p62 mutations in PDB are associated with a reduced level of apoptosis. Furthermore, PDK1, classically involved in the PI3-Akt pathway, maybe important for the p62-zetaPKC pathway leading to NF-kappaB activation and Oc survival

P20

PAGET'S OSTEOSARCOMA IN SCOTLAND

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Background and objectives: Malignant change in established Paget's disease is uncommon. The object of the study was to evaluate the clinico-pathological features and outcome of patients with Paget's osteosarcoma in Scotland.

Methods: A retrospective review was performed using data collected by the Scottish Bone Tumour Registry on patients diagnosed with Paget's osteosarcoma between 1960 and 2004. Information about tumour location, age of diagnosis, gender, lung metastasis, and survival was analysed. Histological slides were reviewed again and the diagnosis of osteosarcoma confirmed. The overall survival was calculated using Kaplan-Meier survival curves.

Results: 78 patients had malignant change in pre-existing Paget's disease. 60 patients had osteosarcoma and 18 malignant fibrous histiocytoma. Average age of diagnosis of Paget's osteosarcoma was 67.8 years with a male to female ratio of 2:1. 27% of cases were within the pelvis. Median survival was 6 months. 30% had lung metastasis at presentation. Since 1960 there has been a gradual decrease in the number of Paget's osteosarcoma seen at the Scottish Bone Tumour Registry.

Conclusion: We present the clinico-pathological features and outcome of patients with Paget's osteosarcoma in Scotland between 1960 and 2004. Pelvic disease and metastasis at presentation reflected the poor outcome in this group of patients. The reason for the apparent decrease in Paget's osteosarcoma in Scotland over the last 40 years is unclear.

P21
ULTRASTRUCTURAL AND IMMUNOCYTOCHEMICAL CHARACTERISATION OF INCLUSIONS IN PAGET'S DISEASE AND RELATED DISORDERS

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Intranuclear and intracytoplasmic 'inclusions' in osteoclasts are a signature of Paget's disease of Bone (PDB), related disorders, such as Familiar Expansile Osteolysis (FEO) and a range of other, late-onset, diseases such as sporadic inclusion body myositis (sIBM) and neuropathies. Although the inclusions in PDB have been well documented at the ultrastructural level (by Transmission Electron Microscopy, TEM), their true composition remains unknown. Inclusions in sIBM and neuropathies have been researched more extensively and are known to contain components of the ubiquitin proteasomal system (UPS), suggesting they contain proteins destined for degradation. To test whether inclusions in osteoclasts in PDB were similar we performed immunohistochemistry with antibodies to UPS components on bone biopsies from PDB patients. We found clear light microscopic (LM) evidence for staining of intranuclear 'inclusions' with ubiquitin and p62/sequestosome-1 and 20S proteasomal subunits. To confirm the inclusions seen in the TEM are indeed the same structures as identified by immunostaining at the LM level immuno-EM studies were required. As suitable tissue samples were not available, we tried to generate 'inclusions' by transfecting HEK293 cells with proteins known to be mutated in PDB (p62) and FEO (RANK). So far, we have not succeeded in recreating the exact PDB inclusions in cellular systems. Overexpression of WTp62 or P392Lp62 leads to formation of cytoplasmic aggresomes (structures associated with removal of misfolded proteins and UPS overload), which contain p62 and other UPS components, while overexpression of FEO-RANK leads to formation of extensive endoplasmic reticulum (OSER), containing RANK. Even though aggresomes and OSER resemble cytoplasmic 'inclusions' by LM, they are very different from PDB inclusions as seen by TEM. However, two additional features: vast areas of intermediate filaments and autophagosomes, both associated with UPS overload, are frequently seen in PDB osteoclasts. Taken together, PDB osteoclasts display many features, including 'inclusions', seen in other diseases associated with defects in the UPS system. Definitive proof of the protein composition of inclusions awaits immuno-EM, or proteomic studies on patient samples, or animal models for the disease. It is plausible that PDB and related disorders are caused by, or associated with, irregularities in the UPS system.

P22
UP-REGULATION OF THE INTERFERON SIGNALING PATHWAYS IN MONOCYTES FROM PATIENTS WITH PAGET'S DISEASE OF BONE

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Genetic components as well as viral factors have been suggested to contribute to the etiopathogenesis of Paget's disease of bone (PD). Peripheral blood monocytes as osteoclast precursors have been shown to display alterations characteristic of gene expressions in osteoclastogenesis. In the present study, we were to investigate the gene expression pattern of pagetic monocytes.

Peripheral blood monocytes were separated from 23 patients (12 males and 11 females) with PD (3 monostotic and 20 polyostotic) aged 41-88 years (mean 61,8 ± 12,2 years) and from 23 age and sex matched helathy subjects. Quantitative real-time PCR was used to monitor gene expression profile of the following genes: GCR, IFNalpha, IFNbeta, IFNgamma, IFNgamma R1, IFNgamma R2, JAK1, p38 MAPK, RANK, STAT1, SQSTM1, STAT2, STAT3, TNFalpha, TRAF6. Serum IFNgamma was measured by ELISA.

The IFNalpha (3,6 ± 0,27), IFNbeta (2,61 ± 0,17), IFNgamma (1,91 ± 0,28), IFNgamma R1 (2,05 ± 0,08), IFNgamma R2 (2,5 ± 0,47), p38 MAPK (2,96 ± 0,32), RANK (1,19 ± 0,07) and STAT1 (2,1 ± 0,16) genes were significantly up-regulated in pagetic monocytes as compared to the healthy controls. GCR (-1,07 ± 0,03) and TNFalpha (-1,95 ± 0,07) genes were significantly down-regulated in PD. The expressions of JAK1 (0,15 ± 0,06), SQSTM1 (-0,01 ± 0,04), STAT2 (-0,08 ± 0,39), STAT3 (0,57 ± 0,25) and TRAF6 (0,14 ± 0,14) were similar in patients with PD and in healthy controls. On the protein level, serum IFNgamma was significantly elevated in patients with PD as compared to healthy controls.

Alterations in the gene expression of genes involved in osteoclastogenesis may help delineate the etiopathogenesis of PD. The involvement of the interferon pathway in Paget's disease warrants for further research.

Roy Altman

Roy D Altman, MD, is Professor of Medicine in the Division of Rheumatology and Immunology at the University of California at Los Angeles. Previously, he was Chief of Rheumatology and Immunology at the University of Miami Miller School of Medicine in Florida.

His research interests have focused on osteoarthritis (animal models, clinical trial design clinical trials) and Paget's disease of bone (the first major clinical trial with etidronate, prevalence in the United States).

With Dr Roland Moskowitz, he has recently edited the fourth edition of Osteoarthritis: Diagnosis and Management. As founder and past President of the Osteoarthritis Research Society International, he started and is Editor-in-Chief of *Osteoarthritis and Cartilage*. He is Editor of *Seminars in Arthritis and Rheumatism*.

Dr Altman is a former board member of the American College of Rheumatology, and served as their AMA Delegate from 1988 to 2003. He is a member of the Board of Trustees and the Medical Advisory Committee of the Paget's Disease Foundation.

Tim Arnett

Tim Arnett graduated with a BSc in Biology from the University of East Anglia and gained his PhD at the Royal Postgraduate Medical School, working in the laboratory of Iain MacIntyre. He held postdoctoral positions at Columbia University and University College London before taking up a lectureship in the Department of Anatomy and Developmental Biology at UCL in 1986. In 1991-92, he undertook sabbatical work at the University of Texas. He was appointed Reader in Mineralised Tissue Biology at UCL in 2001. In addition to his work on the control of osteoclast and osteoblast function by extracellular pH and oxygen, he is interested in the role of extracellular nucleotides in bone. Tim Arnett is a past member of the editorial board of the *Journal of Bone & Mineral Research*, and currently serves on the editorial boards of *Calcified Tissue International* and *Endocrinology*; he was secretary of the Bone Research Society from 2004-7.

Roland Baron

Dr Roland Baron is a Professor in the departments of Orthopedics and Cell Biology at Yale University School of Medicine, since 1977. He received his DDS and PhD degrees from the University of Paris, France. He is the founder and current Editor-in-Chief of Bone, the Official Journal of the International Bone and Mineral Society, and is President-Elect of the European Calcified Tissue Society. Between 1994 and 2002, he also held the position of Vice President and Head of the Bone Diseases Group at Hoechst Marion Roussel and then Aventis. In 2002 he founded ProSkelia, a small pharmaceutical company devoted to the discovery and development of new drugs for bone and hormonal dependent diseases. He has held the positions of President and Chief Scientific Officer of ProSkelia and then ProStrakan, a merger between ProSkelia and Strakan, until April 2006. Dr Baron has published over 250 scientific papers in the field of bone cell and molecular biology.

Teresita Bellido

Dr Bellido obtained a Ph.D. degree in Biochemistry at the Universidad Nacional del Sur, Argentina; and performed postdoctoral training with Stavros Manolagas at Indiana University. In 1994, she was appointed as Research Assistant Professor, in the Endocrinology Division, Department of Internal Medicine, and the Center for Osteoporosis and Metabolic Bone Diseases, at the University of Arkansas for Medical Sciences. And, she was promoted to Research Associate Professor in 2000, to Associate Professor in 2003, and to full Professor with Tenure in 2007.

Throughout her career she have received numerous awards. Her graduate studies in Argentina and postdoctoral training in the US were supported by the Argentinean Research Council (CONICET) through competitive national research fellowships. Her work is has been funded by the National Institutes of Health (NIH) since 1996. She received a R29 First Award in 1996; a K02 Career Development Award in 2000; a R03 in 2005; and a R01 in 2007. In addition, she has been project leader in a Program Project on the Mechanisms of Osteoporosis lead by Dr Stavros Manolagas since 2001 until 2011; and she has also been Co-investigator in projects lead by Dr Robert Jilka on PTH actions in bone and Dr Weinstein on glucocorticoid effects on the skeleton.

Dr Bellido's research focuses on signal transduction in bone cells, with particular interest in the mechanisms of regulation of apoptosis and osteocyte biology. She has published in recognized scientific journals, such as *Cell, Proceedings of the National Academy of Sciences, Science, Journal of Clinical Invesigationt, Endocrinology, Journal of Biological Chemistry, American Journal of Physiology, Journal of Bone and Mineral Research*, and *Bone*.

She is a reviewer for several journals including *Journal of Bone and Mineral Research, Bone, Journal of Biological Chemistry, Endocrinology, American Journal of Physiology*. She is currently a member of the Editorial Board of *Bone*. She reviews extensively for the NIH in the US and for funding agencies of other countries such as the Netherlands, England, Canada and Argentina.

Dr Bellido is also an active member of the American Society for Bone and Mineral Research (ASBMR) for which she has taken volunteer responsibilities in several committes and task forces throughout the years. She is currently chair of the ASBMR Education Committee.

Roger Bouillon

Roger Bouillon is a professor and chairman of endocrinology (internal medicine) at the University and University Hospital of the Catholic University of Leuven in Belgium. He received his medical training in this University and has a Board certification in internal medicine, endocrinology and nuclear medicine (in vitro).

His PhD thesis dealt with calcium and vitamin D metabolism. Hormonal regulation of bone metabolism and vitamin D remained the primary focus of his research although the laboratory of endocrinology (+/- 65 persons) and endocrine clinic is also involved in many other endocrine diseases (especially diabetes and androgens).

He has been Vice-President for Research of the K.U. Leuven and member of the Board of directors of his University and University Hospitals (1995-2005) and is still a member of the Science Advisory Board of the Flemish Government (president of Science Policy Commission). He is a member of the Royal Academy of medicine (Belgium) and a Fellow of the Royal College of Physician (London 2000 - present). He has been the secretary (founding member) and later President of the European Board of Endocrinology (UEMS 1988 - 2002).

He is a member of several European Science Foundation Committees (Board member of the European Medical Research Council) and European Space Agency Life Science working group. He is a Board member (treasurer) of the International Bone and Mineral Society (IBMS) and of the vitamin D workshop Inc.

He is a (co)author of more than 400 peer reviewed articles.

Tim Cundy

Tim Cundy's earliest encounter with Paget's disease was as a medical student at Kings College Hospital in London, where his teachers included Nick Woodhouse and the late Victor Parsons. As a junior doctor at Kings he worked with Ronnie Hamdy; and later as a research fellow in Oxford, John Kanis and Roger Smith were charged with his education. Tim completed his training in endocrinology and diabetes in London, and in 1988 moved to New Zealand, where he now has a personal chair at the University of Auckland. He has published widely on the epidemiology, genetics and treatment of Paget's disease.

David Dempster

Dr Dempster is a Professor of Clinical Pathology at Columbia University in New York and the Director of the Regional Bone Center at the Helen Hayes Hospital in West Haverstraw, NY. Dr Dempster obtained his PhD from the University of Glasgow, and completed postdoctoral studies in Switzerland and France. He has published over 150 research papers on the pathophysiology and treatment of bone disease. Several of Dr Dempster's images of bone structure are on permanent display at the Smithsonian Institution in Washington, DC. He is a Fellow of the Royal Microscopical Society and an active member of the American Society for Bone and Mineral Research, the Endocrine Society, and was a founding member of the International Society of Musculoskeletal and Neuronal Interactions. Dr Dempster was President of the International Society of Bone Morphometry from 1996 to 1999, and serves on the Scientific Advisory Council of the National Osteoporosis Foundation. Dr Dempster is an Associate Editor of *Osteoporosis International*, and has served on the Editorial Boards of *Endocrinology* and the *Journal of Bone and Mineral Research*. He is a member of the Editorial Boards of *Bone* and *The Journal of Clinical Densitometry*.

Patricia Ducy

Patricia Ducy, PhD, is currently an assistant professor in the Department of Pathology at Columbia University (New York, NY, USA). She obtained her PhD from the University Claude Bernard (Lyon, France) and was a postdoctoral fellow in Dr Karsenty laboratory at MD Anderson Cancer Center (Houston, TX, USA) before becoming an assistant professor at Baylor College of Medicine, (Houston, TX, USA). She identified Runx2 as a major regulator of cell differentiation during skeleton development and demonstrated that bone formation is centrally regulated by a leptin-dependent mechanism. Her research uses a combination of molecular biology, mouse genetics, and physiology to analyze the molecular mechanisms controlling bone cell differentiation and functions.

Richard Eastell

Professor Eastell is Professor of Bone Metabolism at the University. He is an Honorary Consultant Physician in metabolic bone disease at the Northern General Hospital, Sheffield. He qualified in medicine from Edinburgh in 1977. He trained at the Mayo Clinic under Dr B L Riggs for 5 years. He became a fellow of the Royal College of Physicians of London in 1996, an honorary fellow of the Royal College of Physicians of Ireland in 1998 and a Fellow of the Royal College of Physicians of Edinburgh, the Royal College of Pathology and the Academy of Medical Sciences in 2000.

He is the head of the Academic Unit of Bone Metabolism Group and has an active research group into the pathophysiology, diagnosis and treatment of osteoporosis. He has published over 200 papers on osteoporosis and related topics. In 1997, he was awarded Hospital Doctor of the Year in the osteoporosis category, in 1998 he was awarded the Corrigan Medal of the Royal College of Physicians of Ireland, and in 2003, was part of the team awarded the Queen's Anniversary Award to the University of Sheffield for the Health and Social Care of Older People. In 2004, he was awarded the Kohn Foundation award from the National Osteoporosis Society and the Society of Endocrinology Medal. He is on the editorial board of *Osteoporosis International*, *Osteoporosis Review*, and *Journal of Clinical Endocrinology and Metabolism*. He is the Past President of the UK Bone Research Society and the President of the European Calcified Tissue Society. He is Chairman of the National Osteoporosis Society.

Paul Emery

Paul Emery is arc Professor of Rheumatology and Head of Academic Unit of Musculoskeletal Medicine University of Leeds and Clinical Director (Rheumatology) at the Leeds Teaching Hospitals Trust in the United Kingdom. Professor Emery is currently the Treasurer of EULAR. He has served on the editorial boards of several journals. He is a recipient of the Roche Biennial Award of Clinical Rheumatology, the Rheumatology Hospital Doctor of the Year award 1999 and EULAR prize 2002 for outstanding contribution to Rheumatology research.

Professor Emery's research interests centre around the immunopathogenesis and immunotherapy of rheumatoid arthritis and connective tissue diseases. He has a special interest in the factors leading to persistent inflammation and is a founder member of ERAS, LEAP (Leeds Early Arthritis Project) and YEAR (Yorkshire Early Arthritis Register) and the Leeds Musculoskeletal Imaging Group. He has published over 500 peer reviewed articles in this area.

Erik Eriksen

Erik Fink Eriksen received his medical degree from Aarhus University, Denmark 1980, where he also finished his specialty training in Endocrinology and Internal Medicine. He defended his Doctor of Medical Science thesis at Aarhus University in 1987 after a 2 year postdoctoral fellowship at the Mayo Clinic 1985-1987. He became consultant in Endocrinology and Internal Medicine at Aarhus Amtssygehus 1994, where he also took the position as Department Head 1995-2001. 2002 he joined Eli Lilly & Co. where he worked as Global Medical Director responsible for the PTH program, until he joined Novartis 2005 as Senior Clinical Consultant and later as Global Brand Medical Director for Aclasta/Reclast.

Concomitant with his clinical activities he led a bone research lab focusing on basic bone biology, calcium metabolism and histomorphometry 1987-2002. His doctoral thesis described a new histomorphometric technique, which enables more detailed investigations of cellular activity in bone biopsies, and at the Mayo Clinic he was a member of the group, which demonstrated the presence of estrogen receptors in bone. In recent years his group has contributed significantly to research around: genetics of osteoporosis, hormonal action on osteoblasts and osteoclasts, immuno-cytochemistry of bone, vitamin D metabolism, regulation of bone remodeling and osteocyte biology.

Erik Fink Eriksen is the author of more than 250 publications and 3 books, 2 of his papers are among the 20 most frequently cited papers published in *Journal of Bone and Mineral Research* over the last 25 years.

Nathalie Franchimont

Nathalie Franchimont, M.D., Ph.D. is the International Medical Affairs Director for osteoporosis in Amgen Inc., Zug , Europe. She supports the program of RANKL inhibition in osteoporosis.

Before joining Amgen Inc. in 2005, Nathalie was Chief of Clinics at the University of Liège, in Liège Belgium, the vice president of the Royal Belgian Society of Rheumatology, and a council member of the European Calcified Tissue Society. She was also a research scientist at the FNRS, the Belgian National Institute for Scientific Research. Her 3-year research training with Ernesto Canalis in Hartford, CT, USA, led to defense of her PhD thesis at the University of Liège. As a rheumatology fellow at Yale University, USA, she develops her interest in the impact of inflammation on bone metabolism for one year. Then, her main focus as a rheumatologist has been the metabolic bone diseases associated with inflammatory diseases. She has conducted basic research projects on targeted genes in osteoporosis and has several outstanding papers in the field. She has also been developing clinical research projects for patients presenting with secondary or post-menopausal osteoporosis, as well as osteonecrosis.

She is an active member of the Belgian Bone Club, the International Bone and Mineral Society and the American Society for Bone and Mineral Research. She has been involved in teaching programs for students, general practitioners, and specialists concerning osteoporosis in her country.

Jim Gallagher

Professor Jim Gallagher holds the Derby Chair of Anatomy at the University of Liverpool and is head of the Department of Human Anatomy and Cell Biology. Jim did his PhD in Cambridge under the supervision of Eric Lawson, and then undertook postdoctoral research in Herbie Fleisch's lab in Bern. He returned to England to work in Graham Russell's lab in Sheffield where along with Jon Beresford, he developed the first techniques to culture cells expressing an osteoblastic phenotype from human bone. His work is focused on elucidating the basic mechanisms underlying human bone and joint disease. Over the past few years, his laboratory has been the international leader in research on the role of extracellular nucleotides and P2 receptors in bone and skin homeostasis. He is founder and director of PalindromX, a biotechnology company devoted to the development of novel diagnostic technologies, and the co-ordinator of "find AKUre", a Europe-wide collaboration to develop new therapeutic strategies for the genetic disorder, alkaptonuria.

Jürg Gasser

Senior Research Investigator, Novartis Institute for Biomedical Research, Musculoskeletal Diseases, Basel, Switzerland

Jürg Gasser is Senior Research Investigator/Scientific Expert at the Novartis Institutes for Biomedical Research (Musculoskeletal Diseases) and Head of an In Vivo Bone Research Laboratory at Novartis Pharma AG in Basel, Switzerland.

The main focus of Dr Gasser's research is the identification of novel bone anabolic targets, based on investigation of the biochemical pathways leading to high bone mass phenotypes in human and murine genetic mutations such as LRP5, and gene expression profiling in response to bone anabolic compounds such as parathyroid and growth hormones. One of his particular areas of interest is the role of the recently discovered pH-sensing receptor in bone. His other research activities include the preclinical characterisation of novel and proprietary pharmaceutical products for the treatment of metabolic bone disease, including cathepsin K inhibitors, oral calcitonin and zoledronic acid.

Dr Gasser is President of the International Society of Musculoskeletal and Neuronal Interactions and a member of the board of directors of the International Society of Bone Morphometry, the International Society of Musculoskeletal and Neuronal Interactions, The Swiss Bone and Mineral Society and the Asia Pacific Society for Bone Morphometry. He has published extensively on

bone biology and morphometry, and the application of non-invasive imaging techniques in animal models of bone disease. Dr Gasser acts as a referee for numerous scientific journals in this field, and is currently the scientific editor of *European Cells and Materials*, associate editor of the *Journal of Musculoskeletal and Neuronal Interactions* and on the editorial board of *Bone*.

David Hosking

David Hosking is a Consultant Physician in the Metabolic Bone Disease service at the City Hospital, Nottingham, UK and until recently was also Professor of Mineral Metabolism in the Department of Biochemistry at the University of Nottingham, UK. He is currently a Visiting Professor at the University of Zagreb, Croatia, and an examiner for the Royal College of Physicians of London. He received his medical training at the University of Birmingham Medical School, Birmingham, UK and post-graduate training in Leiden, Netherlands. Current research interests are in the long term control of Pagets disease and renal bone disease. He has published over 200 papers and book chapters on Pagets Disease, osteoporosis, calcium metabolism and bisphosphonates. He is a member of the Editorial Board of *Osteoporosis International*, the Pagets Foundation in USA (from whom he received the J B Johnson Award for services to Paget's Disease).

Aymen Idris

After graduating from Sunderland University in 1999 with an honour degree in pharmacology, I did my MSc at the University of Aberdeen in Professor G. M. Hawksworth's laboratory. My MSc focused on investigating the Nephrotoxicity of Antibiotics. I moved to the Institute of Medical Sciences to study for a PhD in Professor Stuart Ralston's laboratory. The main focus of my research at this stage was the design and development of small molecule inhibitors of TRAF-dependent signalling as anti-resorptive and anti-rheumatic drugs. I have also identified and demonstrated the role of Cannabinoids on bone metabolism. This work attracted great interest and was recently published in the reputable journal *Nature Medicine*. More recently I moved to the University of Edinburgh working with Professor Stuart Ralston, where I am currently studying the pharmacological actions of Cannabinoids and various novel anti-resorptive and anti-inflammatory drugs. My work is funded by the Arthritis Research Campaign, the Scottish Enterprise, and the Moray Endowments Research Trust. I am also a recipient of ECTS/AMGEN Bone Biology Fellowship.

Virginia Kimonis

Dr Virginia Kimonis is a pediatrician and clinical geneticist. She trained in the UK in family medicine and pediatrics and later developed an interest in genetics in the UAE. Her US training in pediatrics was at Massachusetts General Hospital, and then as a clinical and biochemical genetics fellow at the NIH. Her first academic appointment was at Southern Illinois University Medical School, where she developed an interest in IBMPFD associated with the unusual combination of distal/proximal hereditary inclusion body myopathy, Paget disease of bone and dementia (IBMPFD). Later at Boston Children's Hospital/ Harvard Medical School, she identified VCP (valosin containing protein) as the causative gene. She currently serves as Chief of the Division of Genetics and Metabolism in the Department of Pediatrics at UC Irvine.

Michaela Kneissel

Senior Research Investigator, Novartis Institute for BioMedical Research, Musculoskeletal Diseases, Basel, Switzerland

Michaela Kneissel is Senior Research Investigator I / Novartis Leading Scientist at the Novartis Institutes for BioMedical Research. She is Head of an In Vivo Bone Research Laboratory and a Project Team Leader in the Musculoskeletal Disease Area, Novartis Pharma AG in Basel, Switzerland.

Michaela Kneissel received her Ph.D. from the University of Vienna, Austria. She performed part of her Ph.D. work at the Hard Tissue Research Unit, University College London, UK and was post doctoral fellow at the Radiobiology Division, University of Utah, Salt Lake City, USA before joining Novartis. The main focus of her research is discovery and development of drugs for osteoporosis therapy such as intermittent parathyroid hormone treatment and release. In recent years her research interest centered on the bone formation inhibitor SOST. She has published various papers on bone biology and acts as a referee for diverse scientific journals in this field.

Anne Langston

Anne has a background in Oceanography and Marine Biology in which she received a Masters degree before moving into studies on fish health. Studies on Atlantic salmon led to a doctorate and further employment before moving into human clinical trials - a more logical progression than you might imagine where a highly developed ability to implement good experimental design is required. Anne has considerable experience of leading multi-centre clinical trials and now manages the Edinburgh Clinical Trials Unit at the University of Edinburgh. Of particular relevance is the 6 years experience of research on Paget's disease. She recently relocated from the University of Aberdeen and now works at the University of Edinburgh where she is working on several new studies on Paget's disease. Anne is also a Trustee and Board Committee Member for the National Association for the Relief of Paget's Disease.

David Little

Dr Little graduated MBBS from the University of Sydney in 1986. After selection on the Australian Orthopaedic Association training scheme in 1990 Dr Little graduated FRACS(Orth) in 1994. He undertook fellowships in Paediatric Orthopaedics at the Shriners Hospital for Children in Portland, OR, USA and Texas Scottish Rite Hospital for Children in Dallas TX, USA.

Dr Little commenced on staff at the Children's Hospital, Westmead, when it opened in November 1995. In 1998 he began researching the role of bisphosphonates in distraction osteogenesis and in 1999 officially founded Orthopaedic Research and Biotechnology at CHW. Dr Little remains Head of the Unit, and Deputy Head of the Department of Orthopaedics.

In 2002 Dr Little was an ABC travelling fellow, presenting his research with other international fellows from UK, NZ and South Africa on a six-week tour of North America.

In 2005 Dr Little was awarded his PhD on bisphosphonates in distraction osteogenesis. He has initiated further research on osteonecrosis, fracture healing and the interaction of the anabolic and catabolic responses in bone repair.

Dr Little remains active clinically and is now working on translating pre-clinical work on bone healing to clinical practice.

Kenneth Lyles

Kenneth W. Lyles, MD, is Professor of Medicine and is Director of the Geriatric Physician Fellowship Program at Duke University Medical Center and a member of the Geriatric Research, Education and Clinical Center at the VA Medical Center, Durham, NC.

Dr Lyles received his medical degree from the Medical College of Virginia in Richmond. His postgraduate work included both an internship and a residency in internal medicine at the Medical College of Virginia Hospitals. These positions were followed by a fellowship in endocrinology and metabolism, then a fellowship in geriatrics and gerontology both at the VA and Duke University Medical Centers.

With research focusing on several areas related to bone disease and to aging, Dr Lyles has published extensively in the areas of hip fracture, age-associated osteoporosis, glucocorticoid-induced osteoporosis, Paget's disease, and tumoral calcinosis.

Dr Lyles is a Fellow of the American College of Physicians, the Gerontological Society of America, and the American Geriatrics Society. Active in a number of professional organizations, Dr Lyles currently serves as Secretary-Treasurer of the Paget Foundation. He is Chair Elect 2007 of the Clinical Medicine Section of the Gerontological Society of America. He has served as Deputy Editor for the *Journal of Bone and Mineral Research*. He is now is on the Editorial Boards of the *Journal of the American Geriatrics Society*, *Osteoporosis International*, and *Journal of Gerontology: Medical Science*. He also performs grant reviews for the National Institute of Health, Bureau of Health Professions and Department of Veterans Affairs.

Matthew Gillespie

Associate Professor Matthew Gillespie is an Associate Director of St Vincent's Institute of Medical Research (SVI) in Melbourne, where he is Head of the Bone, Joint and Cancer Unit. His research is focussed on actions of factors derived from breast cancers, and their relevance to breast cancer metastasis in bone, and how T cell-derived cytokines impact upon the formation and resorption of bone.

He has authored over 120 peer-reviewed publications. He is a Member of: the NHMRC Research Committee (Australia); Council and Science Advisory Committee of the Cancer Council of Victoria; Board of Directors of the International Bone and Mineral Society; Board of Directors the Australian and New Zealand Bone and Mineral Society. He is a member of the editorial boards for *Bone, Journal of Bone and Mineral Research*, and is an advisor for the *Journal of Oral Biosciences*.

Ralph Müller

Dr Müller is an Associate Professor of Biomechanics at ETH Zürich. He received his Ph.D. degree in Electrical Engineering from ETH in 1994. In 1996, he moved to Boston where he served as a tenure-track Assistant Professor of Orthopedic Surgery at Harvard Medical School and the Associate Director of the Orthopedic Biomechanics Laboratory. Between 2000 and 2006, he was an SNF Professor of Bioengineering at the Institute for Biomedical Engineering, University and ETH Zürich. The research he has completed and is currently pursuing employs state-of-the-art biomechanical testing and simulation techniques as well as novel bioimaging and visualization strategies for biological tissues. His approaches are now often used for precise phenotypic characterization of tissue response in mammalian genetics, gene therapy and mechanobiology. Dr Müller is an author of over 270 refereed journal and proceeding articles, 1 book, 44 chapters and reviews, and over 250 peer-reviewed abstracts.

Gregory Mundy

Dr Gregory Mundy became the John A. Oates Chair in Translational Medicine Director of the Center for Bone Biology at Vanderbilt University in July 2006. Prior to this appointment, he was Head, Division of Endocrinology and Metabolism (1980-2001) and Deputy and then Interim Director of the San Antonio Cancer Institute at the University of Texas Health Science Center in San Antonio (2001-2006) and Assistant Dean for Clinical Research (2000-2006). Dr Mundy's highly productive and well-funded research program included a National Cancer Institute funded Program Project Grant on the effects of tumors on the skeleton. Current research interests include drug discovery in osteoporosis, the effects of tumors on the skeleton, osteoclast and osteoblast biology and fracture repair. Dr Mundy's publications number more than 500 papers and book chapters. He is the Past-President of the International Bone and Mineral Society and a Past-President of ASBMR. Dr Mundy is a member of both the American Society for Clinical Investigation (ASCI) and the Association of American Physicians (AAP). He has founded two biotechnology startup companies for drug discovery in osteoporosis. He currently serves on the Boards of Directors of the National Osteoporosis Foundation (NOF) and the International Myeloma Foundation. He is in the second percentile of all NIH-funded investigators over the past 25 years.

Brendon Noble

Dr Brendon Noble, Director of the Musculoskeletal Tissue Engineering Collaboration (MTEC), Coordinator of the Scottish Mechanotransduction Consortium (SMTC) and Reader within the Scottish Centre for Regenerative Medicine (SCRM). Dr Noble's interests include osteocyte biology, musculoskeletal regenerative medicine including bone & cartilage repair, tissue engineering, mechanotransduction, human embryonic & adult stem cell based therapies, drug discovery and design & manufacture of tissue engineering scaffolds. He has an international reputation in apoptosis research, and has established laboratories in Edinburgh working on cell responses at the gene and molecular level. Extrusion devices are being used to manufacture novel tissue engineering scaffolds based on a range of materials and finite element modelling to predict mechanical behaviour in situ. He is joint PI on the Scotland wide Scottish Mechanotransduction Consortium. He is PI on an MRC and Geron Corp funded stem cell programme in collaboration with the Roslin Institute and runs a mechanically loaded human bone bioreactor; one of 3 worldwide. Additionally, he runs commercially funded gene therapy projects, fracture repair treatments and drug discovery projects funded by a range of commercial sources.

Jude Onyia

Jude Onyia is the chief scientific leader (CSL) for Integrative Biology at Lilly Research Labs, in Indianapolis, USA. He received his BS degree in forest biology from SUNY Environmental Science and Forestry at Syracuse (1988) and doctorate in cell and molecular biology from the SUNY, Health Science Center at Syracuse (1993). He joined Lilly the same year and since then has made significant contributions in leveraging and integrating biotechnologies (informatics, genomics, proteomics, assay technologies, imaging) to enable and impact drug discovery. His research interests are on the application of systems biology to drug action, targets and biomarkers in multiple disease areas including bone.

Udo Oppermann

Dr Oppermann studied human biology and theoretical medicine at Philipps University, Marburg, Germany and in 1993 completed his PhD with a thesis on "Structural and functional homologies of an evolutionarily conserved class of steroid dehydrogenases and carbonyl reductases". Following work as a research assistant at the Philipps University Department of Pharmacology and Toxicology, Philipps University, Dr Oppermann moved to the Karolinksa Institutet in Stockholm, Sweden, resulting in appointment as Associate Professor in Molecular Biology. In 2003 he spent time as Visiting Scientist at Yale University, New Haven, USA (Department of Developmental and Molecular Biology) and since 2004 Udo Oppermann has been University Research Lecturer; Principal Investigator, Metabolic Enzymes, Structural Genomics Consortium, University of Oxford, UK.

Socrates Papapoulos

Socrates E Papapoulos received his MD from the University of Athens, Greece and he was trained in Internal Medicine and Endocrinology in Athens and at the Middlesex Hospital, London, UK. In 1984 he joined the Department of Endocrinology and Metabolic Diseases of the Leiden University Medical Center where he is currently Professor of Medicine, Consultant Physician and Director of Bone and Mineral Research. Since 1974 he has been continuously engaged in research in disorders of calcium and bone metabolism with special emphasis on the basic and clinical pharmacology of bisphosphonates. Dr Papapoulos is recipient, among other, of the Boy Frame Memorial Award of the American Society for Bone and Mineral Research, the John Haddad Jr Award of the International Bone and Mineral Society, the JB Johnson Award of the Paget's Foundation, USA and he is Doctor Honoris Causa of the University of Athens. Past and present editorial duties include: *Journal of Bone and Mineral Research*, *Bone, Clinical Endocrinology, Osteoporosis International,* Osteoporosis Reports, BONEKey, *Clinical Cases of Mineral and Bone Metabolism, Nature Clinical Practice Endocrinology and Metabolism, Expert Reviews Endocrinology and Metabolism*. He has served on numerous boards and committees including the Board and the Scientific Advisory Board of the International Osteoporosis Foundation, the Board of Directors of International Bone and Mineral Society, the European Union committee for the prevention of osteoporosis, a WHO task force for the development of a world wide strategy for the prevention and treatment of osteoporosis and he is senior scientific advisor of the European Union project Osteoporosis in Europe.

Stuart Ralston

Stuart Ralston graduated in medicine from Glasgow University in 1978 and developed an interest in metabolic bone disease during postgraduate training with Dr Iain T Boyle at Glasgow Royal Infirmary. Professor Ralston trained in general internal medicine and rheumatology in Glasgow between 1981 and 1988. He was appointed as a Wellcome Senior Clinical Research Fellow and Honorary Consultant at the University of Edinburgh between 1988 and 1990 and moved to Aberdeen to take up an appointment as Senior Lecturer in Medicine in 1991. He was appointed as Professor of Medicine and Bone Metabolism in 1996 and was Director of the Institute of Medical Sciences at Aberdeen between 2002 and 2004. Professor Ralston took up the ARC chair of Rheumatology at the University of Edinburgh in February 2005 and was appointed as Head of the School of Molecular and Clinical Medicine in November 2005. He is an Honorary Consultant Rheumatologist with Lothian Health Board and is lead clinician for Osteoporosis services within NHS Lothian.

Professor Ralston has published extensively on several aspects of bone disease including the genetics of osteoporosis; the pathogenesis and management of Paget's disease of bone; the role of Nitric Oxide in bone and the pathogenesis and management of cancer-associated bone disease. He was President of the European Calcified Tissue Society between 1998 and 2005. He is currently

joint editor-in-chief of *Calcified Tissue International*, associate editor of *Bone*; associate editor of *Endocrinology* and a member of the Editorial Board of the *Journal of Bone and Mineral Research*.

Ian Reid

Ian Reid MD is Professor of Medicine and Endocrinology at the University of Auckland, New Zealand. His research interests include the pathogenesis and management of osteoporosis, primary hyperparathyroidism & Paget's disease, and his research group has been active in the identification of novel regulators of bone cell function. He is President of the International Bone and Mineral Society, Secretary of the Asian Pacific Osteoporosis Foundation, and a Fellow of the Royal Society of New Zealand.

René Rizzoli

René Rizzoli is an internist and endocrinologist, with a subspecialty focus on metabolic bone diseases, osteoporosis and disorders of mineral metabolism. He is presently professor of medicine at the University Hospital of Geneva, head of the service of bone diseases of the department of rehabilitation and geriatrics, and chairman of this department. The service of bone diseases is a World Health Organisation collaborating centre for osteoporosis prevention. He is the president of the Swiss Association against Osteoporosis. Dr Rizzoli was chairman of the Committee of Scientific Advisors of the International Osteoporosis Foundation and was chairing the scientific program committee of the IOF World Congress on Osteoporosis. He is presently member of the Executive Committee of the International Osteoporosis Foundation. He is involved in both basic and clinical research projects investigating hormone action, regulation of bone growth, pathophysiology of osteoporosis and the role of nutrition, calcium, protein, bisphosphonates, selective estrogen modulators, parathyroid hormone and strontium ranelate in the prevention and treatment of osteoporosis. Dr Rizzoli is author of more than 400 scientific articles and associate editor of *Bone* and *Osteoporosis International*.

Michael Rogers

Mike Rogers studied Biochemistry in the Department of Molecular Biology & Biotechnology at the University of Sheffield, and remained there for his doctorate studies on the mechanism of action of bisphosphonates. He received his doctorate in 1993 and became the first recipient of the M.D. Francis Research Fellowship in the Department of Human Metabolism & Clinical Biochemistry. In 1997 he was awarded the prestigious JG Graves Medical Research Fellowship from the University of Sheffield, to continue his studies on bisphosphonates and their ability to cause osteoclast apoptosis. In 1997 Mike moved to the University of Aberdeen where he was appointed Lecturer in the Department of Medicine & Therapeutics, then promoted to Senior Lecturer in 1999. In 2003 he was awarded a personal Chair and currently heads a laboratory research group of ~12 people studying the molecular pharmacology of bisphosphonates, the role of the mevalonate pathway in bone metabolism, and small GTPases and other signalling molecules involved in regulating osteoclast activity.

David Roodman

G David Roodman, M.D., Ph.D. is Vice Chair for Research in the Department of Medicine, and Professor of Medicine, Division of Hematology/Oncology, at the University of Pittsburgh School of Medicine. He is Director of the Myeloma Program at the University of Pittsburgh Cancer Institute, and Director of the Center for Bone Biology, at the University of Pittsburgh Medical Center. Dr Roodman received his Ph.D. in Biochemistry from the University of Kentucky, and did post-doctoral work at the University of Minnesota.

Currently, Dr Roodman holds two U.S. patents, three investigator initiated NIH grants, and heads a Program Project Grant on the "Pathobiology of Paget's Disease. This Program Project attempts to answer several important questions about the role measles virus plays in pathophysiology of Paget's disease and the important role the genetic component plays in the pathologic process. The Department of Veterans Affairs Merit Review Grant and the Multiple Myeloma Research Foundation's Collaborative Program Grant entitled "Bone Microenvironment Factors in Myeloma Bone Disease", also fund him.

Dr Roodman serves on several peer review editorial boards, including *Experimental Hematology, Bone, Journal of Clinical Investigation*, *Endocrinology*, and is an Associate Editor for the *Journal of Bone and Mineral Research*.

Kuber Sampath

Dr T Kuber Sampath is a graduate of Madras University, and vice president for discovery research initiative at Genzyme Incorporation, MA. Previously, Dr Sampath held positions as vice president for research at Selective Genetics, Inc, San Diego, CA and most recently as executive director of research and development at Creative BioMolecules Inc, Hopkinton, MA. Dr Sampath was responsible for the discovery and therapeutic development of Company's (in collaboration with Stryker, Kalamazoo, MI) lead product, recombinant human bone morphogenetic protein BMP-7/OP-1 (OP-1TM). The product is now been used in USA, Canada, Europe and Australia as bone graft substitute for orthopedic repair. Prior to that, Dr Sampath worked as visiting scientist in bone cell biology section at National Institutes Dental Research, National Institutes of Health Bethesda, MD where he made original contributions for the identification of proteins responsible for the "bone morphogenetic activity". To this end, Dr Sampath published more than 110 papers in leading research journals and co-invented more than 95 issued US, European and Japan patents. Dr Sampath is one of the founding scientists on bone morphogenetic protein field and a pioneer in the field of therapeutic tissue engineering, and has been elected as a member in several US and international scientific societies and have given several invited plenary lectures throughout the world.

Andrew Sewell

Andrew Sewell knows very little about bone biology. He has recently taken up a position as Distinguished Research Professor at Cardiff University School of Medicine. He also continues as a visiting scientist at the Peter Medawar Building for Pathogen Research in Oxford. He has been a Wellcome Trust Senior Fellow since 2001. Professor Sewell's research focuses on the adaptive immune system and in particular T cell immunity. His interests concentrate around the molecular recognition of T cell antigens and include T cell-mediated immunity to pathogens and cancer in addition to autoimmune T cells.

Scott Simonet

Scott received his Ph.D. in Molecular Biology and Biochemistry from the University of South Florida, College of Medicine in 1988. He subsequently received an Individual National Research Service Award from the NIH to perform postdoctoral training at the Gladstone Foundation Laboratories for Cardiovascular Disease at the University of California, San Francisco, where he studied regulation of apolipoprotein gene expression with John Taylor and Bob Mahley.

Scott came to Amgen as a Research Scientist in February of 1992 and began to search for secreted proteins, which might have therapeutic utility. In 1994 he was part of a group contributing to Amgen's Genomics program that identified and functionated a secreted protein in the TNFR Superfamily that we called Osteoprotegerin (OPG). This group showed that OPG was a critical regulator of bone mineral density and acts by inhibiting the actions of RANKL on osteoclastogenesis. In 1998, this work received an award from the American Society of Bone and Mineral Research for Outstanding Research on the Pathophysiology of Osteoporosis.

Scott is currently Executive Director of the Bone and Mineral Metabolism Research group in the Department of Metabolic Disorders at Amgen. He heads a group of 52 scientists working on developing novel therapies for osteoporosis, end-stage renal disease, and other bone related diseases.

Dwight Towler

Dwight A Towler received his MD/PhD from Washington University in St. Louis. His thesis work delineated the enzymology of eukaryotic protein N-myristoylation. He completed residency and metabolism fellowship at Barnes-Jewish Hospital. Dr Towler's NIH-supported research emphasizes transcription factor biology and vascular endocrinology relevant to diabetic arterial calcification. In addition to his academic career, Dr Towler spent 4 years in industry, most recently as Senior Director of Bone Biology and Osteoporosis Research at Merck. Clinically, he specializes in bone and mineral diseases. His work has been recognized by the Charles E. Culpeper Foundation (1996), the ASBMR (Fuller Albright Award 2000), and the American Society for Clinical Investigation (elected 2004). He holds membership on the editorial boards for JBMR and Bone, and the NIH Skeletal Biology Development and Disease study section. Dr Towler is currently the. Lang Professor of Medicine and Director of Bone and Mineral Diseases at Washington University.

Slobodan Vukicevic

Slobodan Vukicevic, MD, PhD is a full professor and head of the Laboratory of Mineralized Tissues at the School of Medicine, University of Zagreb, Zagreb, Croatia. His scientific interest includes isolation, characterization and function of bone and cartilage morphogenetic proteins, signal transduction mechanisms in osteoblasts and chondrocytes, discovery of new biomarkers, biological regeneration of tissues with particular interest in bone, cartilage and kidney. He received several awards for achievements in science; was organizer of five international conferences and is the president of the Croatian Calcified Tissue Society, a member of the World Academy of Arts and Sciences (WAAS) and a member of the European Molecular Biology Organization (EMBO). He has authored more than 130 papers and six books.

Michael Whyte

Michael P Whyte, M.D., is Professor of Medicine, Pediatrics, and Genetics at Washington University School of Medicine, St. Louis and is on staff at Barnes-Jewish Hospital, St. Louis Children's Hospital, and Shriners Hospital for Children in St. Louis. He is Medical-Scientific Director of the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospital.

Dr Whyte earned his M.D. degree at Downstate College of Medicine, State University of New York, Brooklyn, New York and than had internship and residency training in Internal Medicine at Bellevue Hospital in New York City before spending two years as Clinical Associate at the National Institutes of Health, Bethesda, Maryland. After fellowship in Endocrinology, he joined the faculty of Washington University School of Medicine, St. Louis.

Dr Whyte's research interests include the cause and treatment of especially heritable skeletal disorders in children and adults. Included are genetic forms of rickets such as hypophosphatasia and X-linked hypophosphatemia, brittle bone diseases like osteogenesis imperfecta, and conditions that cause dense bones such as osteopetrosis. Collaborative laboratory investigations include mapping of specific diseases on human chromosomes and then searches for mutated genes. Molecular findings are then related to clinical observations to better understand how these conditions develop. The Research Center at Shriners Hospital serves as a national resource for diagnosis, treatment, and investigation of disorders of bone and mineral metabolism and skeletal dysplasias in children. Dr Whyte has authored or coauthored more than 280 scientific papers or book chapters concerning pediatric and adult metabolic bone diseases.

GENERAL INFORMATION

Accommodation

If you are staying at the University please collect your room key from the Porters' Lodge on your arrival, otherwise please go straight to the registration desk.

Vacating rooms

For those staying on campus, please note that rooms must be vacated after breakfast on the day of your departure.

Luggage storage

Luggage can be stored in the Porters' Lodge.

Contact information - during the conference

In case of emergencies, messages can be left for delegates at the Porters' Lodge on +44 (0)1865 271700. The Porters' Lodge is manned 24 hours a day.

Registration

The registration desk is in the Porters' Lodge and is open as follows:

Monday 9 July	15.00-19.00
Tuesday 10 July	08.00-17.00
Wednesday 10 July	08.00-17.00
Thursday 12 July	08.00-17.00
Friday 13 July	08.00-17.00

Conference Office

Please visit the Conference Office in Room B, upstairs in the Bernard Sunley Building, if you have any queries during the meeting.

Internet access

Please see the staff at the registration desk or the Conference Office for details.

Meals on campus

Dining times at the College are as follows:

07.45 breakfast

12.45 lunch *(or as stated in the scientific programme)*

19.00-20.30 dinner *(Monday, Tuesday, Thursday & Friday)*

19.30 for 20.00 dinner *(Wednesday)*

Lectures take place in the **Bernard Sunley Lecture Theatre** and posters, exhibition and tea/coffee breaks will be in the same building.

Social events

MONDAY 9 JULY, 19.00
Dinner in St Catherine's College dining hall

TUESDAY 10 JULY, 19.00
Dinner in St Catherine's College dining hall

TUESDAY 10 JULY, 20.15
Post-dinner walking tour featuring some of Oxford's most historic pubs. Please meet at the Porters' Lodge

WEDNESDAY 11 JULY, 19.30 - MIDNIGHT
Banquet in St Catherine's College dining hall

THURSDAY 12 JULY, 19.00
Dinner in St Catherine's College dining hall

FRIDAY 13 JULY, 19.00
Dinner in St Catherine's College dining hall

Car parking

Please be sure to display a permit if you are parking in the College car park. Permits can be picked up at the Porters' Lodge.

Taxis

Telephone numbers for taxis:

Courtesy Cars:01865 874787 or 873497
ABC Taxis:01865 770077 or 775577
Radio Cars: 01865 242424

COLLEGE PLAN