4th International Workshop on Advances in the Molecular Pharmacology and Therapeutics of Bone Disease
6-8 July 2009

and

International Symposium on Paget's Disease
8-9 July 2009

St Catherine's College
Oxford, UK

Final Programme

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Contents

Advances in the Molecular Pharmacology and Therapeutics of Bone Disease

Scientific Committee

Chairman:
Graham Russell (Oxford, UK)

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Cyrus Cooper (Oxford and Southampton, UK)
Jack Martin (Melbourne, Australia)

International Symposium on Paget's Disease

Scientific Committee

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INTRODUCTION

We offer you a very warm welcome to Oxford and to this meeting, which is the 4th in a series devoted to "Advances in the Molecular Pharmacology and Therapeutics of Bone Disease". These meetings have been held at 2 yearly intervals in conjunction with the International Symposium on Paget's Disease, under the auspices of the National Association for the Relief of Paget's Disease, which was founded as a UK medical charity over 30 years ago.

The workshop on molecular pharmacology is designed to review and discuss some of the recent advances in the genetics, cell biology, biochemistry and pharmacology of bone. This is intended to provide a basis not only for understanding the molecular mechanisms of action of drugs already known to act on the skeleton, but also to provide a rational basis for developing novel therapies in the future. The workshop continues to involve scientists engaged in drug discovery and the pharmacology of bone, as well as clinical scientists involved in translating this new knowledge into clinical practice.

A highlight of this year's meeting is a celebration of the 40th anniversary of the discovery of the biological effects of the bisphosphonates. The key publications were published in *Science* in 1969, with the first clinical trials of bisphosphonates in Paget's disease following in Oxford shortly afterwards. Even now, the bisphosphonates are still the leading drugs used for the treatment of bone diseases, including Paget's disease.

This celebration will include a presentation from Sir Julian Paget, the great grandson of Sir James Paget, who first described Paget's disease of bone in 1876.

Paget's disease remains a challenging and enigmatic disorder affecting a substantial proportion of the adult population in many countries. Paget's disease can now be effectively treated and many of its distressing and disabling complications prevented. The meeting will bring together international experts to discuss the latest advances in knowledge, with particular emphasis on advances in epidemiology, genetics and treatment.

The meeting is again held at St Catherine's College, which combines an attractive college setting and ample opportunity for interactions among colleagues. We wish you an enjoyable and memorable meeting**.**

Graham Russell
Chairman

PROGRAMME

Sunday 5 July

19:00 Welcome dinner at Wadham College

Monday 6 July

09:15-09:45 Coffee

09:45 Welcome and introduction to Oxford and the programme
Chairs: Andy Carr/ Cyrus Cooper/Graham Russell (Oxford, UK)

10:00-11:30 Introduction and update on bone biology and genetics: 1

Chairs: Stephen Krane (Boston, USA)/Greg Mundy (Nashville, USA)

10:00 THE INTEGRATION OF OSTEOBLAST AND OSTEOCLAST FUNCTION
Jack Martin (Melbourne, Australia)

10:30 THE INTERRELATIONSHIP BETWEEN OSTEOBLAST AND ADIPOCYTE DEVELOPMENT
Cliff Rosen (Maine, USA)

11:00 THE ROLE OF WNT SIGNALLING AND OESTROGEN RECEPTORS IN MECHANOTRANSDUCTION
Joanna Price (London, UK)

11:30 Break

11:45-12:45 Introduction and update on bone biology and genetics: 2

Chairs: Miep Helfrich (Aberdeen, UK)/Michael Whyte (St Louis, USA)

11:45 GENETIC DISORDERS OF SKELETAL DEVELOPMENT
Francis Glorieux (Montreal, Canada)

12:15 LESSONS FROM GENETIC DISORDERS OF CALCIUM METABOLISM
Raj Thakker (Oxford, UK)

12:45 Lunch

14:00-15:30 Cellular regulation of bone metabolism

Chairs: Tim Arnett (London, UK)/Tim Skerry (Sheffield, UK)

14:00 OSTEOCYTE BIOLOGY
Lynda Bonewald (Kansas City, USA)

14:30 COUPLING MECHANISMS AND CYTOKINES
Natalie Sims (Melbourne, Australia)

15:00 BONE AS A METABOLIC REGULATOR
Gerard Karsenty (New York, USA)

15:30 Break and attended posters (PhD students)

16:00-17:40 Current and emerging therapeutic approaches to bone metabolism: 1

Chairs: Jill Cornish (Auckland, New Zealand)/David Roodman (Pittsburgh, USA)

16:00 PROSTANOIDS: NEW USES IN BONE REPAIR
Vishwas Paralkar (Groton, USA)

16:25 NEW CLASSES OF ANABOLICS
Aymen Idris (Edinburgh, UK)

16:50 SIRTUINS: LINKING AGING AND BONE LOSS
James Edwards (Nashville, USA)

17:15 CALCITONIN LIVES ON!!
Morten Karsdal (Herlev, Denmark)

17:40 Close

Tuesday 7 July

09:00-10:45 Current and emerging therapeutic approaches to bone metabolism: 2

Chairs: Jim Gallagher (Liverpool, UK)/Jonathan Reeve (Cambridge, UK)

09:00 Historical introduction to PTH as a therapeutic
Jonathan Reeve (Cambridge, UK)

09:15 SYSTEMIC AND LOCAL ACTIONS OF PTH AND PTHRP AND THEIR RELEVANCE TO THERAPEUTICS
David Goltzman (Montreal, Canada)

09:45 PTH AND INTERACTIONS AMONG BONE-ACTIVE DRUGS
Serge Ferrari (Geneva, Switzerland)

10:15 THE CALCIUM-SENSING RECEPTOR AS A THERAPEUTIC TARGET: WHERE NEXT?
Ed Nemeth (Toronto, Canada)

10:45 Coffee

11:15-12:45 Current and emerging therapeutic approaches to bone metabolism: 3

Chairs: Philippe Clézardin (Lyon, France)/Michael McClung (Oregon, USA)

11:15 SERUM SEROTONIN AS A REGULATOR OF BONE FORMATION
Patricia Ducy (New York, USA)

11:45 CATHEPSIN K - A THERAPEUTIC TARGET FOR OSTEOPOROSIS
Sevgi Rodan (Philadelphia, USA)

12:15 SARMS AND VITAMIN D ANALOGUES
Henry Bryant (Indianapolis, USA)

12:45 Lunch

14:00-15:30 Current and emerging therapeutic approaches to bone metabolism: 4

Chairs: Serge Ferrari (Geneva, Switzerland)/Afsie Sabokbar (Oxford, UK)

14:00 SERMS AND LASOFOXIFENE
Richard Eastell (Sheffield, UK)

14:30 PHARMACOLOGY OF THE RANK/RANK LIGAND SYSTEM
Paul Kostenuik (Thousand Oaks, USA)

15.00 CLINICAL USES OF DENOSUMAB
Nathalie Franchimont (Zug, Switzerland)

15:30 Break and attended posters (PhD students)

16:00-17:30 Current and emerging therapeutic approaches to bone metabolism: 5

Chairs: Richard Eastell (Sheffield, UK)/Bente Langdahl (Aarhus, Denmark)

16:00 SCLEROSTIN: BIOLOGY AND THERAPEUTIC POTENTIAL
Michaela Kneissel (Basle, Switzerland)

16.30 UNRAVELLING THE STRONTIUM STORY
Eugene McCloskey (Sheffield, UK)

17:00 THERAPEUTIC OPTIONS IN OSTEOPOROSIS: UNRESOLVED ISSUES
Erik Eriksen (Oslo, Norway)

17:30 Close

Wednesday 8 July

09:00-11.00 New approaches and future prospects

Chairs: Dennis Black (San Francisco, USA)/Ian Reid (Auckland, New Zealand)

09:00 ADVANCES IN THE IMAGING OF BONE
Clemens Löwik (Leiden, Netherlands)

09:30 GENETICS OF COMPLEX DISORDERS, INCLUDING OSTEOPOROSIS
Matthew Brown (Brisbane, Australia)

10:00 STRUCTURAL BIOLOGY, EPIGENETICS and DRUG DISCOVERY
Udo Oppermann (Oxford, UK)

10.30 THE FUTURE OF BONE RESEARCH AND OSTEOPOROSIS THERAPY
Sundeep Khosla (Rochester, USA)

11.00 Coffee

11:30-13.00 Future prospects

Chairs: Andy Carr (Oxford, UK)/Raj Thakker (Oxford, UK)

11:30 THERAPEUTIC TARGETTING IN BONE: ENZYME REPLACEMENT IN HYPOPHOSPHATASIA
Michael Whyte (St Louis, USA)

12:00 SKELETAL REGENERATION AND THE THERAPEUTIC POTENTIAL OF BMPs
Slobodan Vukicevic (Zagreb, Croatia)

12:30 FUNDING MUSCULOSKELETAL RESEARCH IN THE OBAMA ERA: "YES WE CAN!"
Joan McGowan (Bethesda, USA)

13.00 Lunch

14:00-16:00 Bisphosphonates 40th Anniversary celebration sessions

Chairs: Cyrus Cooper (Oxford, UK)/Jack Martin (Melbourne, Australia)/Graham Russell (Oxford, UK)

14:00 INTRODUCTION
Graham Russell (Oxford, UK)

14:10 THE LEIDEN EXPERIENCE: 1970s ONWARDS
Socrates Papapoulos (Leiden, Netherlands)

14:35 LESSONS FROM CHEMISTRY
Hal Ebetino (Cincinnati, USA)

15:00 KNOWNS AND UNKNOWNS IN THE MECHANISMS OF ACTION OF BISPHOSPHONATES
Mike Rogers (Aberdeen, UK)

15:25 ORTHOPAEDIC APPLICATIONS
David Little (Sydney, Australia)

15:50 TEA TIME REFLECTIONS
Stephan Korte (Novartis, Basel) and **Henry van den Berg** (P&G, Cincinnati)

16:00 Bisphosphonates Anniversary Tea Party!

17:00-18:00 Plenary lectures

Chairs: Michael Hooper (Sydney, Australia) /Marilyn McCallum (NARPD)/Peter Selby (Manchester, UK)

17.00 THE PAGET DYNASTY
Sir Julian Paget

17:30 WHAT HAVE WE LEARNT ABOUT PAGET'S DISEASE OF BONE FROM THE STUDY OF ARCHAEOLOGICAL SKELETONS
Simon Mays (English Heritage and Southampton, UK)

Thursday 9 July

09:00-10:20 Pathogenesis of Paget's Disease and Clinical Studies: 1

Chairs: Bill Fraser (Liverpool, UK)/Caje Moniz (London, UK)

09:00 PAGET'S DISEASE: PARADIGMS, PUZZLES AND PARADOXES
Tim Cundy (Auckland, New Zealand)

09:25 THE PRISM TRIAL AND ZIPP STUDY
Stuart Ralston (Edinburgh, UK)

09:50 EXPERIMENTAL STUDIES IN PAGET'S DISEASE
David Roodman (Pittsburgh, USA)

10:20 Coffee and attended posters

10:50-12:45 Pathogenesis of Paget's Disease and Clinical Studies: 2

Chairs: Geoff Nicholson (Melbourne, Australia)/Johann Ringe (Cologne, Germany)

10:50 GENETIC BASIS OF PAGET'S DISEASE
Wim Van Hul (Antwerp, Belgium)

11:15 ANIMAL MODELS OF PAGET'S DISEASE
Anna Daroszewska (Edinburgh, UK)

Oral Communications: Pathogenesis and Genetics

Chairs: Stuart Ralston (Edinburgh, UK)/Mike Stone (Cardiff, UK)

11:40 P16
IDENTIFICATION OF NOVEL GENETIC VARIANTS THAT PREDISPOSE TO PAGET'S DISEASE OF BONE BY GENOME WIDE ASSOCIATION
Omar Olbagha (Edinburgh, UK)

11:45 P07
CONTRIBUTION OF TNFRSF11A (RANK) POLYMORPHISMS TO THE RISK FOR SPORADIC PAGET'S DISEASE OF BONE IN 3 EUROPEAN POPULATIONS
PYJ Chung (Antwerp, Belgium)

11:55 P22
HETEROZYGOUS VERSUS HOMOZYGOUS EXPRESSION OF MUTANT RANK PROTEINS ASSOCIATED WITH EARLY ONSET FORMS OF PAGETS DISEASE
D Mellis (Aberdeen, UK)

12:00 P23
HIGH LEVEL EXPRESSION OF INCLUSION-ASSOCIATED PROTEINS IN PAGET'S DISEASE OF BONE
Miep Helfrich (Aberdeen, UK)

12:05 P10, P11, P12
DO OSTEOBLASTS CONTRIBUTE TO THE DEVELOPMENT OF PAGET'S DISEASE?
Brya Matthews (Auckland, New Zealand)

12:15 P18
THE ROLE OF OSTEOCLASTOGENIC FACTORS IN PAGET'S DISEASE
F Jones (Oxford, UK)

12:20 P13
THE RELATIONSHIP BETWEEN SQSTM1 PROTEIN FUNCTION, NF-{KAPPA}B SIGNALLING AND PAGET'S DISEASE SEVERITY
Robert Layfield (Nottingham, UK)

Oral Communications: Clinical Studies

Chairs: Michael Davie (Oswestry, UK)/Terry O'Neill (Manchester, UK)

12:25 P25
PAGET'S DISEASE OF BONE: ANALYSIS OF 134 CASES IN A SMALL ISLAND IN THE SOUTH OF BRAZIL
G Heiden (Santa Catarina, Brazil)

12:30 P06
LARGE COLLABORATIVE STUDY ON GEOGRAPHIC VARIATION OF SQSTM1 MUTATIONS IN PAGET'S DISEASE OF BONE IN ITALY
Luigi Gennari (Siena, Italy)

12:40 P04
CARDIOVASCULAR RISK IN PATIENTS WITH PAGET DISEASE OF BONE. A DISEASE WITH AN ADVANTAGEOUS CARDIOVASCULAR PROFILE?
L Corral-Gudino (Salamanca, Spain)

12:45 Lunch

13.30-14.00 Attended posters

14:00-15:30 Treatment of Paget's Disease

Oral Communications: Treatment

Chairs: Michael Davie (Oswestry, UK)/Terry O'Neill (Manchester, UK)

14:00 P05
COMPARISON OF INTRAVENOUS AND INTRAMUSCULAR NERIDRONATE REGIMENS FOR THE TREATMENT OF PAGET'S DISEASE OF BONE
D Merlotti (Siena, Italy)

14:10 P24
LONG-TERM REMISSION OF PAGET'S DISEASE AFTER INDUCTION OF REMISSION WITH ORAL ALENDRONATE: A FIFTEEN-YEAR FOLLOW-UP STUDY
Geoff Nicholson (Geelong, Australia)

14:20 P14
DOMICILARY TREATMENT OF PAGET'S DISEASE OF BONE WITH BISPHOSPHONATES
Keatley Adams (Bolton, UK)

14:30-15:30 **Paget's Disease: Treatment and Clinical Studies**

Chairs: Ken Lyles (Durham, USA)/Roger Smith (Oxford, UK)

14:30 LONG-TERM EFFICACY OF ZOLEDRONIC ACID COMPARED WITH RISEDRONATE IN PAGET'S DISEASE: 5 YEAR FOLLOW UP
Ian Reid (Auckland, NZ)

15.00 PAGET'S DISEASE: THEN AND NOW
David Hosking (Nottingham, UK)

15:30 Closing Remarks

International Symposium on Paget's Disease

SUBMITTED ABSTRACTS

P01

PAGET'S DISEASE: PARADIGMS, PUZZLES AND PARADOXES

T Cundy*[1]

[1]*University of Auckland, New Zealand*

As a clinical entity, Paget's disease has been recognised for over 130 years. In the early 20th century, developments in radiography, histology and biochemistry (particularly the measurement of alkaline phosphatise activity) increased our understanding of its pathophysiology, and the late 20th century saw great advances in treatment, but a full understanding of its etiology remains elusive. The modern era has brought many significant advances in understanding, in particular an appreciation of the importance of genetic factors, which explain the tendency of Paget's disease to run in families and its epidemiological associations with migration from western Europe. However, many puzzling features remain unexplained. These include the focal nature of the disease, its apparently simultaneous appearance at random skeletal sites and the decline in disease severity and prevalence that has become apparent in recent decades. Part of our problem in understanding Paget's disease is that there is no directly comparable human or animal disorder. Experimental approaches have included the introduction of putative disease-associated viruses into bone cells, and the introduction of human disease-associated SQSTM1 mutations into the genome of laboratory animals. These experiments have been varyingly successful in replicating some features of Paget's disease, but not the full human phenotype. In many respects Paget's disease behaves like a benign multifocal tumour, so a full understanding of the molecular mechanisms involved may lie with some of the newer approaches to tumour biology.

P02

OCULAR MANIFESTATIONS OF JUVENILE PAGET'S DISEASE

NM Kerr[1], H Cassinelli[2], L DiMeglio[3], C Tau[4], B Tüyzüs[5], T Cundy*[6], AL Vincent[1]

[1]*Department of Ophthalmology, Faculty of Medical and Health Sciences, University of Auckland,* [2]*Endocrinologia, Hospital de Niños, Buenos Aires, Argentina,* [3]*Riley Hospital for Children, Indiana University School of Medicine, USA,* [4]*Endocrinología, Hospital de Pediatría Garrahan, Buenos Aires, Argentina,* [5]*Department of Pediatrics, Istanbul University, Istanbul, Turkey* [6]*Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, New Zealand*

Juvenile Paget's disease (JPD) is a rare metabolic bone disorder characterised by extremely rapid bone turnover, that results from deletion of or mutations in the gene for osteoprotegerin. A characteristic retinopathy and even cases of blindness have been described in some patients. The aim of this study was to determine the prevalence of retinopathy in JPD, to characterise the spectrum of retinal changes that may occur and to summarise the available literature.

Patients with JPD were recruited from local and international centres. Patients underwent an ophthalmic assessment consisting of a minimum of visual acuity and either dilated fundal examination or colour fundus photography. A MEDLINE literature search was performed and all identified case reports were reviewed for information regarding the ocular phenotype. We devised a scoring system, based on the cumulative number of abnormal findings, to grade the severity of the retinopathy.

Seven patients with JPD were examined, and all but one had retinal abnormalities. Descriptions of ocular manifestations in a further 12 patients were identified in the literature. JPD is associated with a distinctive retinopathy characterised by mottling of the retinal pigment epithelium, peripapillary atrophy, angioid streaks, and choroidal neovascularisation. The cumulative retinal score was strongly correlated with age (Spearman $r = 0.79$, $p<0.001$).

Retinal changes are probably present in the majority of patients and can progress to severe visual loss. The findings suggest that abnormalities in osteoprotegerin or its signalling pathway are implicated in the calcification of Bruch's membrane and the pathogenesis of angioid streaks.

P03

P392L MUTATION IN AN ITALIAN PEDIGREE WITH PAGET'S DISEASE OF BONE: ONE AFFECTED AND NINE ASYMTPOMATIC MUTANT CARRIERS, FIVE OF WHOM WITH AGE OVER 50 YEARS

AF Falchetti, F Marini, L Masi, A Amedei, D Strigoli, F Cioppi, A. Tanini, ML Brandi*

Department of Internal Medicine, University of Florence, Florence, Italy

In the last year, we clinically identified a 74 years old male subject affected by polyostotic Paget's disease of bone (PDB). He gave his informed consent for genetic analysis of p62/SQSTM1 gene and we found him to be carrier of the P392L germline mutation. After a genetic counselling, 14 members of his family from three (FI-FIII) generations, (4 sisters and 1 brother FI, 2 daughters FII, 5 nephews FII, 1 grandchild FIII, and a son of one nephew FIII) accepted

to perform genetic test. Overall, their age range was 11-72 years and specifically the age range of FI was from 56 to 72 years, FII from 44 to 51 years, and FIII from 11 to 17 years. Nine subjects carry P392L: the 4 sisters (61-72 years), 1 daughter (51 years), 3 nephews (44-49 years), and the son of one nephew (17 years). None of them exhibited clinical signs or symptoms or history clearly suggestive for PDB, and none is currently performing antiresorptive therapy. All but the son of one nephew accepted to perform bone turnover screening, including the evaluation of bone alkaline phosphatase. The results were negative in all the members with the exception of inadequate serum levels of 25OHD in 2 individuals, readily supplied with cholecalciferol. Different genotype-phenotype analyses have shown a high penetrance for p62/SQSTM1 mutations, with 90 to 100% of gene carriers within families having developed the disease by the age of 65 years. Currently, the 3 FI mutant female carriers are older than 65 years of age, the fourth one is a 62 years old female, and they have not been exhibiting any biochemical and/or clinical evidence suggestive for PDB, suggesting an incomplete penetrance of the mutation or a delayed onset of PDB. To address these issues, an annual biochemical screening of bone turnover in the mutant carriers is expected. Moreover, in order to study more accurately their bone phenotype we have recently proposed to them to perform a total body bone scintigraphy in order to detect possible minimal skeletal affected foci and 6/9 have given their consent. We are currently waiting for their bone scans.

P04

CARDIOVASCULAR RISK IN PATIENTS WITH PAGET DISEASE OF BONE. A DISEASE WITH AN ADVANTAGEOUS CARDIOVASCULAR PROFILE?

J García-Aparicio[1], L Corral-Gudino[1], J del Pino-Montes[2], M Alonso-Garrido[3], R González Sarmiento[3], AT Vega-Alonso[4]*

[1]Servicio de Medicina Interna, Hospital Universitario de Salamanca, Spain; [2]Servicio de Reumatología, Hospital Universitario de Salamanca, Spain; [3]Unidad de Medicina Molecular, Departamento de Medicina, Universidad de Salamanca, Spain; [4]Observatorio de Salud Pública, Dirección General de Salud Pública y Consumo, Consejería de Sanidad, Valladolid, Spain

BACKGROUND:

Because patients with Paget Disease of Bone (PDB) had more frequently medial arterial or arteriosclerotic calcification than controls, there is a widespread belief that they have a high cardiovascular risk.

The objectives of this study are a) estimate PDB cardiovascular risk, b) compare PDB vs non PDB risk.

METHODS:

We included PDB patients attended in our hospital. A cardiovascular risk assessment was performed at physician offices between February 1, 2008 and June 31, 2008. Ten-year coronary risk was determined using 2 equations; Framingham and REGICOR (REG1, REG2, REG3). Ten-year cardiovascular risk was determined using SCORE algorithm.

The control group were selected from Cardiovascular Risk in Castilla y León study. This register consist of a representative sample of 4.012 patients. Two control were selected for each PDB patient according age, gender and origin.

RESULTS:

One hundred and twenty PDB patients were studied. Fifty eight were male, with a mean age of 70 years old. Two hundred and twenty six control were selected.

Seven percent of PDB patients had diabetes mellitus, 23 % had systemic hypertension and 2.7 % were smoker vs 19.9 %, 54.7 % and 12.5 % in the control group (p = 0.002, p = 0.000 and p = 0.000 respectively). Mean cholesterol was 198.73 ± 33.96 mg/dl in PDB patients vs 218.68 ± 37.4 mg/dl in control group (p 0.000).

Two (2.9 %) PDB patients had high-risk (>20 %) according Framingham equation vs 43 (25.1 %) patients in the control group (p = 0.000). Two (2.9 %), none and none PDB patients had high risk according the three cut-off points of REGICOR; REG1 (> 10 %), REG2, (> 15 %) and REG3 (> 20 %) vs 51 (30.2 %), 17 (10.1 %) and 11 (6.5 %) in the control group (p = 0.000, p = 0.000 and p = 0.000 respectively). One (1.8%) PDB had high-risk (> 5 %) according SCORE vs 12 (5.3 %) patients in the control group (p = 0.215).

CONCLUSION:

Our study suggests that PDB patients have a better cardiovascular profile and a low 10-year coronary and cardiovascular risk than general population.

P05

COMPARISON OF INTRAVENOUS AND INTRAMUSCULAR NERIDRONATE REGIMENS FOR THE TREATMENT OF PAGET'S DISEASE OF BONE

D Merlotti[1], D Rendina[2], G Mossetti[2], L Gennari[1], G De Filippo[2], G Martini[1], A Avanzati[1], P Strazzullo[2], R. Nuti[1]*

[1]Internal Medicine, Endocrine-Metabolic Sciences and Biochemistry, University of Siena, Siena, Italy; [2]Department of Clinical and Experimental Medicine, Federico II University of Naples, Naples, Italy

Aminobisphosphonates represent the most common treatment for Paget's disease of bone (PDB), with the potential for sustained remission. Intravenous regimens demonstrated improved efficacy and compliance with respect to oral regimens. Recently, we demonstrated that zoledronate (4 mg) and neridronate (200 mg), single

intravenous infusion, had a similar efficacy in achieving biochemical remission at 6 and 12 months in up to 90% of patients non-responders to pamidronate. In this study we compared the effects of a same neridronate dose (200 mg) given as intravenous (iv) (100 mg for 2 consecutive days) or intramuscular (im) (25 mg once a week for 1 month) in 56 patients with active PDB. Randomization was stratified according to baseline total alkaline phosphatase (ALP) levels and previous bisphosphonate treatment. All patients were advised to receive calcium plus vitamin D throughout the study period. Blood samples were collected at baseline and after 3, 6, 12 months. The primary efficacy end-point was the therapeutic response at 6 months, defined as normalization of ALP levels or a reduction of at least 75% in total ALP excess. Serum levels of bone ALP, crosslaps, and 25-hydroxyvitamin D (25OH-D) were also measured. A significant 40-50% decrease in ALP levels was observed with both regimens after 3 months. At 6 months, 92% and 96% of patients receiving iv and im neridronate, respectively had a therapeutic response. Normalization of ALP levels at 6 months was achieved in 89% and 93% of patients in iv and im neridronate groups, respectively. Interestingly, the response to treatment was significantly correlated with baseline ALP and 25OH-D levels at 6 months. The decrease in ALP levels was highest in patients with higher baseline total or bone ALP levels and with higher 25OH-D levels at 6 months. Normalization in ALP levels was maintained at 12 months in 81.5% and 83% of patients, in iv and im groups, respectively. Both regimens were well tolerated with an acute phase response of 11-13%. In conclusion, both im and iv neridronate regimens (cumulative dose of 200 mg/year) showed a similar efficacy in achieving biochemical remission in up to 90% of patients with active PDB.

P06

LARGE COLLABORATIVE STUDY ON GEOGRAPHIC VARIATION OF SQSTM1 MUTATIONS IN PAGET'S DISEASE OF BONE IN ITALY

L Gennari[1], F Gianfrancesco[2], M Di Stefano[3], D Rendina[4], D Merlotti[1], T Esposito[2], A Aloia[2], G Martini[1], M Mazzetti[3], S Gallone[5], I Rainero[5], L Pinessi[5], G Isaia[3], P Strazzullo[4], R Nuti[1], G. Mossetti[4]*

[1]Internal Medicine, Endocrine-Metabolic Sciences and Biochemistry, University of Siena, Siena, Italy, [2]Institute of Genetics and Biophysics, CNR, Naples, Italy, [3]Internal Medicine, University of Turin, Turin, Italy, [4]Clinical and Experimental Medicine, Federico II University of Naples, Naples, Italy, [5]Neuroscience, University of Turin, Turin, Italy

Paget's disease of bone (PDB) is a chronic disease of the skeleton with a consistent genetic component. The geographic distribution of PDB is not uniform, with a higher prevalence of the disease in populations of British descent. Moreover increased prevalence areas have been described in different Countries. We recently characterized an area of increased prevalence of PDB in the region of Campania, in Southern Italy. Patients from this region also showed increased severity of disease with peculiar phenotypic characteristics and an increased number of familial cases. In this study we examined the clinical characteristics, and the prevalence and type of SQSTM1 mutations in a large sample of 560 unrelated PDB subjects from several regions including 164 patients from Campania. This sample also included 3 families with PDB associated with giant cell tumor. Eleven different mutations in SQSTM1 gene were observed in 33% and 11% of familial and sporadic PDB cases, respectively. Two of these mutations, M401V, and A427D, were novel and have not been previously described. The other mutations (Y383X, P387L, P392L, E396X, M404V, G411S, D423X, G425E, G425R) have been previously described. An higher prevalence of SQSTM1 mutations was observed in polyostotic than monostotic cases. The distribution of mutations in this sample was more heterogeneous than in other countries, particularly in the high prevalence area of Campania. In keeping with previous studies, the P392L was however the most common observed mutation. Genotype-phenotype analysis confirmed an increased severity of disease and an earlier age of onset in mutations that insert a stop codon. Interestingly, in PDB subjects from Campania a different distribution and a significantly reduced prevalence of mutations in familial cases was observed with respect to the other regions, despite an increase in disease severity. Moreover SQSTM1 mutations were not observed in the 3 kindreds in which the disorder was associated with giant cell tumors. This might imply the presence of mutations in different genes as well an increased persistence of a possible environmental trigger, or both these conditions.

P07

CONTRIBUTION OF TNFRSF11A (RANK) POLYMORPHISMS TO THE RISK FOR SPORADIC PAGET'S DISEASE OF BONE IN 3 EUROPEAN POPULATIONS

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Paget's Disease of Bone (PDB) is a late-onset metabolic bone disorder with an abnormal bone remodeling, affecting up to 5% of Caucasians (>55y). In bone remodeling, RANK (receptor activator of nuclear factor-kappaB), encoded by TNFRSF11A, plays a key role. Moreover, PDB-like diseases (familial expansile osteolysis, expansile skeletal hyperphosphatasia and early onset PDB) and an osteoclast-poor form of osteopetrosis are due to TNFRSF11A mutations. Yet, the role of TNFRSF11A in classical PDB has not been investigated in detail.

Firstly, association study was performed in the Belgian population: 196 sporadic PDB patients (83 females,112 males) and 212 controls (86 females, 126 males). SNP selection in and around the TNFRSF11A gene was based on HapMap (27 tagSNPs, 5 multimarker tests 'MMTs') and NCBI (rs35211496, H141Y). Genotyping was carried out by KASPar technique, TaqMan assay and direct sequencing. Statistics shows that 13 SNPs and 3 MMTs are significantly associated (P-values between 0.036 and 3.17E-4), majority of them due to an association in the female subcohort. Six SNPs and 1 MMT withstand the Bonferroni correction (P<0.002).

Secondly, replication was performed with 2 non-synonymous SNPs (H141Y and A192V) in 1) a Dutch cohort with 79 cases (35 females, 43 males) and 95 controls (46 females, 49 males) and 2) a British cohort with 308 cases (144 females, 138 males) and 326 controls (166 females, 159 males). Statistics of both populations shows significant P-values for both SNPs: H141Y with P=0.012 & P=0.028 (respectively); and A192V with P=8.8E-5 & P=0.005 (respectively). Although the H141Y association seems to be driven only by females (the Dutch: P=0.004, the British: P=0.047), significance of A192V is observed in males as well as in females (the Dutch: P=0.012 & P=0.002, respectively; the British: P=0.047 & P=0.045, respectively).

Finally, meta-analysis of all 3 European populations results in P=4.73E-8 for A192V (common OR of C allele=1.575, 95%CI: 1.339-1.852) and P=0.004 for H141Y (common OR of C allele=1.374, 95%CI: 1.111-1.700).

In conclusion, these results provide a very strong indication that TNFRSF11A SNPs influence the risk to develop sporadic PDB. Ongoing functional studies will elucidate whether any of the non-synonymous SNPs is the real causative SNP.

P08

Abstract withdrawn

P09

Abstract withdrawn

P10

DO OSTEOBLASTS CONTRIBUTE TO THE DEVELOPMENT OF PAGET'S DISEASE?

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Paget's disease is a common bone disease characterised by focal regions of accelerated bone turnover. Pagetic osteoclasts are grossly abnormal and have been considered to drive the disease, but bone formation is also abnormal suggesting osteoblast involvement. We have cultured osteoblasts and bone marrow from 23 patients with Paget's disease, and from non-pagetic bone from patients with and without the disease. RNA from these cells has been used to identify changes in gene expression between pagetic and non-pagetic cells using microarrays and real time PCR. Previously we reported that pagetic cells had an unchanged RANKL/OPG ratio, increased interleukin 6, DKK1, and alkaline phosphatase, and decreased osteocalcin and bone sialoprotein expression. In the current study we used low density array-based real time PCR analysis to further investigate differential gene expression in pagetic osteoblasts and bone marrow cells.

mRNA levels of a number of genes with important roles in osteoblast differentiation and function were significantly down-regulated in the pagetic osteoblasts. These included the master regulator of bone formation, RUNX2, and two additional transcription factors, DLX5 and SATB2. Fibroblast growth factor receptor 2, which mediates signals that promote osteoblastic proliferation and differentiation was also down-regulated in pagetic osteoblasts. BMP2, a potent stimulator of bone formation and tenascin C, an extracellular protein that influences cell morphology were also down-regulated. Genes significantly up-regulated in pagetic osteoblasts included

matrix gla protein, an inhibitor of mineralisation that is normally down-regulated during osteoblast differentiation, and the chemokine monocyte chemotactic protein 1, which is induced by various factors including interleukin 6, and can stimulate monocyte recruitment and osteoclastogenesis.

Taken together with results from our previous studies, it appears that osteoblasts derived from pagetic lesions are less differentiated than osteoblasts from healthy bone, and produce lower levels of important osteoblastic factors and higher levels of local factors that increase osteoclastogenesis. The osteoblasts retain their abnormal phenotype despite being removed from the pagetic bone microenvironment for a number of weeks, suggesting that there is a primary abnormality in pagetic osteoblasts and they play an important role in the development of the pagetic lesion.

P11

CELLULAR MORPHOLOGY OF CULTURED PAGETIC OSTEOBLASTS

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Paget's disease of bone is characterised by focal areas of disorganised bone architecture resulting from abnormal and increased bone turnover. In the lytic phase of Paget's disease the overactive pagetic osteoclast is thought to commence the cycle of abnormal bone turnover by increasing bone resorption which is then followed by concomitant increased bone formation by surrounding osteoblasts (sclerotic phase). The initiating microenvironment and factors involved in the development of this disease are still unknown. It is well established that during normal bone remodelling osteoblasts regulate osteoclast differentiation and activity. For this reason we have studied the pagetic osteoblast and its potential role in the development of Paget's disease. A number of genes were found to have differential expression when pagetic osteoblasts were compared to osteoblasts cultured from healthy bone (1). To further investigate pagetic osteoblasts, transmission electron microscopy (TEM) was used to examine the ultrastructure of these bone cells.

Trabecular bone explants from seven individuals with Paget's disease and three individuals without Paget's disease were collected during joint replacement surgery. All pagetic bone samples were confirmed to be from pagetic sites by x-ray or scintigraphy. Primary osteoblast outgrowth cultures from pagetic and non-pagetic trabecular bone explants were grown in culture flasks until near confluency. Following trypsinisation, isolated osteoblasts were cultured on plastic discs for several days and these osteoblast covered discs were then processed for examination by TEM following standard procedures. Several individual osteoblasts were examined from each of the 10 patients on a TecnaiTM G2 Spirit TWIN transmission electron microscope. Non-pagetic osteoblasts displayed typical and expected ultrastructural features. In comparison, pagetic osteoblasts contained extensive rough endoplasmic reticulum (RER) in long multiple and parallel arrays, and vesicles were frequently larger and more abundant.

These morphological changes, taken together with the demonstration of changes in gene expression in pagetic osteoblasts, suggest that these cells may be contributing to the pathogenesis of Paget's disease.

1. Naot D, et al JBMR 2007; 22:298-309.

P12

KERATIN 18 IS OVER-EXPRESSED IN OSTEOBLASTS DERIVED FROM PAGETIC LESIONS BUT IS NOT INVOLVED IN THE FORMATION OF DISRUPTED (MINERALISED) MATRIX

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Paget's disease is a common focal bone disorder. Pagetic lesions, which result from over-activity of osteoclasts and osteoblasts, appear lytic at early stages and later turn sclerotic, with areas of irregular, disorganised bone matrix. Pagetic osteoclasts are grossly abnormal, and have been the focus of most of the research on the cellular mechanisms of Paget's. Given the tight coupling between osteoclasts and osteoblasts, we characterised the pagetic osteoblast, investigating possible changes that could contribute to Paget's. We compared gene expression in osteoblasts and bone marrow cells from pagetic and non-pagetic patients. Microarray analysis identified a number of differentially regulated genes, and the intermediate filament protein keratin 18 (KRT18) was one of the most highly upregulated genes in pagetic osteoblasts. Real-time RT-PCR comparing 28 pagetic samples to 49 controls confirmed that KRT18 expression is more than three times higher in pagetic cells. In the present study we investigated the effects of KRT18 over-expression on osteoblasts and mesenchymal cells.

Primary human osteoblasts were transduced with a KRT18 adenoviral vector and compared to cells transduced with

a control vector. Real-time RT-PCR showed that KRT18 over-expressing cells have increased levels of alkaline phosphatase, FGF2 and the chemokine MCP1, genes that had previously been identified by the microarrays as up-regulated in pagetic osteoblasts. In order to study the possible effects of KRT18 over-expression on cell morphology and extracellular matrix formation, we cultured virally transduced human primary mesenchymal cells in 3-dimentianal collagen scaffolds. The scaffolds provide an extracellular structure which resembles the bone environment and is therefore better suited for the study of cell morphology and matrix formation and mineralisation. Cells and matrix were analysed using confocal imaging. Cells were also studied by staining for alkaline phosphates activity, alizarin red to measure calcium deposition and 'Osteochromebone' stain which identifies cells, osteoid and mineralised bone. Cultures of KRT18 over-expressing cells were not significantly different from the controls.

In conclusion, these results suggest that KRT18 plays a role in osteoblast biology, and overexpression of this gene can reproduce some of the features of pagetic osteoblasts, however, this does not appear to include the disrupted matrix formation.

P13

THE RELATIONSHIP BETWEEN SQSTM1 PROTEIN FUNCTION, NF-{KAPPA}B SIGNALLING AND PAGET'S DISEASE SEVERITY

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Mutations affecting the SQSTM1 gene are a common cause of Paget's disease of bone (PDB). We have previously shown that many PDB mutations, which cluster within the UBA domain of SQSTM1, manifest their effects by reducing the binding affinity of the protein for its interaction partner, ubiquitin. At the cellular level, SQSTM1 mutations result in dysregulated NF-{KAPPA}B signalling which may underlie increases in osteoclast activity. It is our hypothesis that for UBA domain mutations, the magnitude of change in the ubiquitin-binding affinity of the mutant SQSTM1 protein is directly related to its ability to regulate NF-{KAPPA}B signalling and by extension disease severity in PDB patients. To test elements of this hypothesis, we have generated 'artificial' mutations within the UBA domain of SQSTM1 which exhibit a higher binding affinity for ubiquitin than the wild type sequence. In reporter assays, SQSTM1 constructs containing these changes inhibit NF-{KAPPA}B signalling to a greater degree than wild type, whereas PDB mutants (with reduced ubiquitin-binding affinity) produce a level of activation of NF-{KAPPA}B signalling greater than wild type, providing support for the hypothesis. These 'artificial' mutations appear to exert their effects by affecting the natural oligomerisation state of the SQSTM1 UBA domain which presumably regulates normal ubiquitin-binding function. In the future, correlating SQSTM1 protein function with aspects of disease phenotype may help explain the wide variation in disease severity in PDB patients.

P14

DOMICILARY TREATMENTOF PAGET'S DISEASE OF BONE WITH BISPHOSPHONATES

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Intravenous Bisphosphonates are an effective and safe treatment for Paget's disease of bone. They are widely used, generally given in hospital day units with associated inconvenience to patients. In Bolton we have pioneered the administration of iv bisphosphonates in the patient's home, via the nursing staff of our Rapid Response Team. This has been the case for 14 years for iv Pamidronate. This was started because of significant delays in patients being treated as day cases because of bed pressures. Recently we have commenced the use of home iv Zoledronic acid.

The decision to treat is made by a consultant rheumatologist, GPwSI or advanced rheumatology practitioner, who refers to the Rapid Response Team. A mutually agreeable treatment date is arranged. The infusion is given in the home, with nursing staff present, 60 minutes for Pamidronate (1mg/min) every two weeks for three treatments and over 15 minutes for 5mg of Zoledronic acid once.

To date over 200 patients involving 500 domiciliary visits by the Rapid Response Team have been treated. All patients complete a satisfaction questionnaire post infusion, as well as being asked to document adverse effects. Feedback is very positive with excellent patient satisfaction e.g.)I dislike going to hospital, this service was excellent for me.

Practical exclusions from the service include poor venous access, or patient choice, as well as the usual clinical exclusions. There have been no serious adverse reactions, no cases of osteonecrosis of the jaw or deaths. This service also avoids the risk of hospital acquired infection. Patients who are intolerant to oral treatment and have poor venous access are treated with inhaled calcitonin. The availability of Zoledronic acid has greatly decreasing the use of Pamidronate

Conclusion: This service is appreciated by patients, is convenient for patients, and is in keeping with progression to health care nearer home.

P15

ACCEPTABILITY OF GENETIC TESTING AND PREVENTATIVE TREATMENT IN PAGET'S DISEASE: PSYCHOLOGICAL AND CLINICAL PREDICTORS

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Paget's disease of bone (PDB) is a common condition, affecting about 3% of individuals over the age of 55 years in the UK. Genetic factors such as SQSTM1 play an important role with mutations in the gene responsible for about 50% of cases of familial PDB. These mutations are highly penetrant, >90% of carriers develop the disease by the age of 65 years. This knowledge might be translated into clinical practice by offering subjects who carry SQSTM1 mutations prophylactic therapy in an attempt to prevent the disease, or complications developing. However the acceptability of this novel therapeutic approach needed to be established. This project used behavioural science models to investigate acceptability.

A postal questionnaire of non-affected relatives of people with PDB was conducted. The sample included relatives of PDB patients with and without a family history of PDB. The questionnaire explored a range of factors including: illness representations; treatment representations; demographic details; family environment; and beliefs of other people.

Questionnaires were completed by 175 non-affected relatives (aged 18-86) of people with PDB. Acceptability for taking a genetic test was high (mean intention: 6.2 on a 1-7 scale) as was receiving treatment (mean intention: 5.7). These results show that it would be feasible to implement a programme of genetic testing and targeted intervention for PDB. The accessibility of the genetic test and treatment are strong determinants for the acceptability of the treatment programme, and it can be deduced from this that these determinants would affect eventual uptake of and commitment to the testing and treatment programme. Strong preferences exist for the test and any subsequent treatment to be carried out in primary care rather than in a hospital environment. There were also interesting preferences for the nature of the preventive treatment. Whilst a once-a-week tablet was acceptable to a high proportion of respondents, an annual intravenous infusion was more so. This illustrates a need to develop a genetic testing service in the primary care sector, and to then test the effectiveness of preventive treatment with a bisphosphonate such as Aclasta, a potent bisphosphonate that requires a single infusion at infrequent intervals.

P16

IDENTIFICATION OF NOVEL GENETIC VARIANTS THAT PREDISPOSE TO PAGET'S DISEASE OF BONE BY GENOME WIDE ASSOCIATION

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Paget's disease of bone (PDB) is a common disorder that affects up to 3.1% of individuals over the age of 55 in the UK. PDB is characterised by focal abnormalities of bone turnover, which lead to clinical symptoms of bone pain, deformity, deafness, osteoarthritis and pathological fractures. Genetic factors are important in PDB but so far only one gene (SQSTM1) has been confirmed to predispose to classical PDB. Mutations of SQSTM1 are found in about 10% of patients with sporadic PDB and 40% with familial PDB indicating that other predisposing genes remain to be identified. In this study we sought to identify novel genetic variants that predispose to PDB by genome wide association study. The study population comprised 750 patients with PDB in whom SQSTM1 mutations had been excluded by DNA sequencing and 1000 unaffected controls. Approximately 104 patients (14%) had a positive family history of PDB. Genotyping for 318,237 single nucleotide polymorphism (SNP) was performed using Illumina hapmap300 chip. Quality control procedures were performed on the data to exclude SNP and samples with low call rate, low genotype quality score, non-Caucasian ancestry, and individuals who were related. Data analysis was performed using the

Cochran-Mantel-Haenszel test adjusting for population structure. Three genomic regions were identified to be significantly associated with PDB after adjusting for genomic inflation and genome-wide multiple testing (Bonferroni). These were located on chromosome 1, 10, and 18 with p values of 1.1 x 10-11, 1.0 x 10-8, and 2.6 x 10-10, respectively. Four Additional loci were identified with possible evidence of association with PDB (p< 1 x 10-6) on chromosomes 2, 5, 8 and 12. Work is in progress to validate these loci in independent set of cases and controls and identify the causative genetic variants.

As well as advance our understanding of the pathogenesis of PDB, the genetic variants we have identified may have value as diagnostic markers for disease susceptibility and severity. The causal genes and their associated signalling pathways may also represent new targets for the design of new drugs to treat PDB.

P17

DESIGN OF AN INTERNATIONAL, RANDOMISED TRIAL OF TARGETED ZOLEDRONIC ACID THERAPY TO PREVENT SQSTM1 MEDIATED PAGET'S DISEASE.

THE ZIPP TRIAL

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Background

Paget's disease of bone (PDB) is characterised by increased bone turnover affecting one or multiple bones. Mutations in the SQSTM1 gene have been identified in 20-50% affected individuals with a positive family history Bisphosphonates are highly effective at suppressing elevated bone turnover but are of limited benefit in patients who have already developed complications.

Trial objective

In this study, we will test the hypothesis that genetic testing coupled with prophylactic treatment with Zoledronic acid can prevent the development of raised bone turnover and focal bone lesions in carriers of SQSTM1 mutations.

Trial design

The trial will consist of two phases: (1) Individuals with PDB are consented for mutation analysis of the SQSTM1 gene. If a mutation is identified, their eligible relatives (>30 years old without PDB) who have not yet developed clinical signs of PDB, will be offered genetic testing for the mutation. Those found to carry the mutation will be invited to take part in the intervention study. (2) The unaffected carriers are randomised into either a biochemical marker sub-study or a bone-lesion sub-study and given an infusion of placebo or Zoledronic acid (infusion repeated after 30 months). Biochemical markers of bone turnover will be analysed yearly for 5 years. The development of new bone lesions will be assessed by radionuclide bone scan after 5 years. The effects of the intervention on bone pain and quality of life will also be studied.

Results

The results of this study may underpin the introduction of a programme of genetic testing and targeted intervention for familial PDB into routine clinical practice

P18

THE ROLE OF OSTEOCLASTOGENIC FACTORS IN PAGET'S DISEASE

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Paget's disease is a focal bone disorder characterised by numerous, large overactive osteoclasts. Osteoclasts form from circulating mononuclear precursors in the presence of M-CSF, a macrophage survival and proliferation factor, and RANKL, a key growth factor required for osteoclast formation. It is thought that Pagetic osteoclasts are exposed to high levels of M-CSF and are hypersensitive to RANKL, promoting excessive osteoclast differentiation and activation. A number of other growth factors are able to partially substitute for either M-CSF or RANKL to induce osteoclastogenesis. In this study we investigated the effect of several M-CSF and RANKL substitutes on osteoclast differentiation and formation in Paget's disease.

Peripheral blood mononuclear cells (PBMC) were extracted from five blood samples and cultured on coverslips/dentine slices for 14 and 21 days respectively in the presence of either M-CSF (25ng/ml), RANKL (50ng/ml), the RANKL substitutes (LIGHT (50ng/ml), APRIL (25ng/ml), BAFF (25ng/ml), NGF (25ng/ml)), or the M-CSF substitutes (HGF(25ng/ml), VEGF(25ng/ml)).

Of the M-CSF and RANKL substitutes LIGHT consistently produced the greatest amount of resorption (on average 78%) relative to the positive control (M-CSF/RANKL). LIGHT-induced resorption was less in the bisphosphonate treated patients.

Serum levels of LIGHT, APRIL, BAFF, and VEGF were measured by ELISA in 16 patients. We found no difference in LIGHT (50-60pg/ml) or APRIL (4000-6000pg/ml) levels as compared to the age-matched controls. We observed higher levels of VEGF in the untreated patients and those untreated for a number of months (230-280pg/ml) as compared to the bisphosphonate treated patients and age-matched controls (30-70pg/ml).
Our results indicate that some M-CSF and RANKL substitutes are present at increased concentrations (e.g. VEGF) in Paget's disease. LIGHT also plays a clear role in Paget's disease by inducing high levels of resorption that are affected by bisphosphonate treatment. Further investigation into the full effect of LIGHT on Pagetic osteoclast differentiation and formation will help to clarify its role in Paget's disease.

P19

INTEREST OF 18F-FLUORIDE POSITRON EMISSION TOMOGRAPHY FOR ASSESSMENT AND MANAGEMENT OF MONOSTOTIC PAGET'S DISEASE OF BONE

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Introduction: Paget disease of bone (PDB) is characterized by focal areas of increased bone metabolism. In monostotic PDB, the biochemical parameters of bone remodelling are frequently comprised in the normal range. Therapeutic response is therefore difficult to assess. We tested PET scan for assessing PDB response to therapy.
Materials: Fourteen patients suffering from monostotic PDB were prospectively followed-up prior to, 1, 6 and 12 months after bisphosphonate (BP) therapy. Six patients with polyostotic PDB served as controls. PET scan values of the involved bone were expressed as Ki and SUVmax, with comparison with the contralateral normal bone.
Results: In monostotic cases, values of biological parameters normal or slightly elevated at the start decreased significantly after BP therapy, although within the narrow normal ranges, impairing the follow-up in individual cases. No significant change in the PET values was observed after therapy on the healthy bone. On the PDB side, however, a significant decrease versus time was observed, with the nadir observed at 6 months in monostotic PDB. No PET value of a pagetic bone reached normalization comparatively with the normal contralateral bone.
Conclusion: 18F-Fluoride PET scan can assess metabolic activity in monostotic PDB. Response to therapy is evident already after 1 month, contrary to the biological data, but the local pagetic lesion remains metabolically active. If PET technique becomes readily available, it represents a new tool to assess metabolic activity in monostotic PDB in which the parameters of bone remodeling are of poor help.

P20

PAGET'S DISEASE OF BONE: IMAGERY OF THE AXIAL AFFECTATION

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The finding of scintigraphic images suggesting Paget Disease (PD), described in the literature as: heart and clover signs, provide to the scintigraphic study a highly specificity in the disease diagnosis.
Objective: To evaluate the possible temporal sequence of such vertebral scintigraphic images in patients with axial PD diagnosed, taking into account the vertebral segment involved the initial radiological phase, disease activity, alterations of the vertebral static, and the presence or absence of associated antiresorptive therapy.
Material and Methods: We selected patients with axial skeleton involvement secondary to PD classified as clover and heart signs in vertebral scintigraphic images.
We performed the intra- and interobserver concordance analysis to confirm the diagnosis and identify sequential changes in the scintigraphic images.
Results: Kappa index 95% CI = 1
From a total of 335 patients affected by PD, 53 were selected for presenting a clover and/or heart sign on scintigraphic vertebral images.
45 showed a clover image, 6 presented a heart image and 2 had both images simultaneously.
The distribution of the 53 patients regarding to radiological vertebral location was: 30 patients lumbar spine involvement, 7 patients dorsal spine, 10 patients showed dorso-lumbar distribution and 1 patient cervico-lumbar.
In 5 patients no change was found in the radiological phase but their vertebral level showed a scintigraphic uptake.
The most frequent radiological phase was the mixed one, observed in 36 patients, with predominant location at the lumbar spine. The scintigraphy detected an uptake in all patients in the study: 29 patients had lumbar involvement, 11 presented dorsal location, the dorso-lumbar involvement and cervico-lumbar spine was observed in 12 patients and in 1, respectively. Those patients with heart on scintigraphic image, showed a sclerotic phase in conventional radiology (100%), regardless of the affected vertebral location and scintigraphic distribution, showing a significant trend.
Conclusions: In spite of not evidencing the existence of a temporal sequence of these scintigraphic uptakes in

patients affected by axial PD, it has been found the presence of correlation between the scintigraphic image and the radiologic phase, as well as showing a preferential location for the different radiological phases and scintigraphic distributions.

P21

PAGET DISEASE OF BONE: EFFECT OF ZOLEDRONIC ACID ON PHOSPHO-CALCIUM METABOLISM AND MARKERS OF BONE TURNOVER

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In preclinical and clinical trials have demonstrated the great bone antiresorptive capacity of zoledronic acid (ZA) showing significant biological and clinical implications in the treatment of Paget's disease (PD)

Objective: To assess the biological and scintigraphic effect of ZA in patients with active and resistant PD.

Methods: Fifty patients with active PD were included, from department of rheumatology, conducted between June2006 and December2008

Each patient received a single 5 mg infusion of ZA (15-minute period).

The following variables were collected: demographic data, scintigraphic distribution, phospho-calcium metabolism and biochemical markers of bone turnover.

Biochemical markers were measured at baseline and 15, 30, 60, 180 days postinfusion.

The primary end point: the proportion of patients who had a therapeutic response and the percentage of change in biochemical markers of bone turnover respect to baseline values

Results: 50 patients with PD active were included. The scintigraphic distribution: polyostotic (62%)/monostotic (38%).

The percentage of patients who had a therapeutic response 2 months after the drug administration was one hundred per cent, with the persistence of these effects during the six months of follow-up. sTAP levels showed a more rapid and marked reduction, remaining into a normal range during the six months of follow-up. Despite presenting a similar pattern, the bALP levels showed an early reduction, remaining into a normal range during the follow-up. Median percent reductions in NTx were similar in magnitude to those observed for sTAP levels and were maximal in the first 15 days.

An increase of PTHi levels was observed 15 days after the infusion, remaining higher than usual during the three first months, becoming normal afterwards. Only 15 patients remained higher during six months of follow-up with normal 25OHVitD, phospo-calcium values

The scintigraphic uptake (baseline/6m post-infusion): decrease (76.7%), absence (23.3%)

The most frequent side effect was a flu-like syndrome (30% of the patients)

Those patients who did not show these clinical manifestations were treated with statines, probably these drugs are involved in the mevalonate pathway

Conclusions: A single infusion of ZA provided a significantly greater therapeutic response of the biochemical markers of bone turnover and scintigraphic activity, short-medium term.

P22

HETEROZYGOUS VERSUS HOMOZYGOUS EXPRESSION OF MUTANT RANK PROTEINS ASSOCIATED WITH EARLY ONSET FORMS OF PAGETS DISEASE

DJ Mellis, KI Shennan, A Duthie, JG Greenhorn, MH Helfrich, MJ Rogers and JC Crockett*

Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK

Early onset Pagets disease of bone, Familial Expansile Osteolysis (FEO) and Expansile Skeletal

Hyperphosphatasia are conditions featuring overactive osteoclasts, associated with heterozygous insertion mutations in the signal peptide region of the receptor activator of NFkB (RANK) gene. The aim of this study is to investigate whether these mutations lead to abnormal sub-cellular trafficking of the RANK receptor.

Over-expressing FEORANK by adenoviral transduction in mouse osteoclast precursors resulted in a significant increase in the number of mature osteoclasts formed compared to precursors transduced with wildtype (WT)RANK. To determine how the mutant form of RANK stimulates osteoclast formation, the localisation of mutant RANK was investigated. In human osteoclasts, immunostaining and confocal microscopic analysis demonstrated that, when overexpressed alone, FEORANK accumulated within circular structures in the cytosol and could not be detected at the plasma membrane. Transmission electron microscopy revealed the presence of organised smooth endoplasmic reticulum (OSER) in osteoclasts over-expressing FEORANK, but not in cells over-expressing WTRANK. These data were supported by in-vitro translation experiments demonstrating that the signal peptide of RANK is not cleaved in the mutant forms of the RANK protein, while cleavage of the signal peptide was detected in WTRANK. Taken together with our previous observations demonstrating lack of RANKL-dependent signalling in cells expressing these mutant RANK proteins, these data strongly suggest that these are inactivating mutations.

By contrast to homozygous expression of FEORANK, when co-expressed with WTRANK (to mimic the heterozygous situation in patients) in 293 cells, FEORANK shared a similar localisation to WTRANK.

Collectively, these results demonstrate that important functional differences exist following homozygous or heterozygous expression of the proteins. We hypothesise that lack of signal peptide cleavage in the disease-associated mutants effectively converts RANK into a resident ER protein, altering its ability to traffic to the plasma membrane. However, co-expression of FEORANK with WTRANK appears to rescue this phenotype, perhaps allowing mutant RANK to reach the plasma membrane by associating with WTRANK. The precise nature of this association and how this results in increased osteoclast formation and resorption is currently under investigation.

P23

HIGH LEVEL EXPRESSION OF INCLUSION-ASSOCIATED PROTEINS IN PAGET'S DISEASE OF BONE

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Osteoclasts in Paget's disease of bone (PDB) have long been known to contain ultrastructurally identifiable inclusion bodies, which appear identical to those seen in other inclusion body diseases, such as inclusion body myositis. Interestingly in the disease IBMPFD (inclusion body myositis, paget's disease and frontotemporal dementia) inclusions have been found in both muscle and osteoclasts. Because of the presence of these inclusions we have postulated that PDB is an "inclusion body disease", or a "conformational disease". We have used immunohistochemical staining to assess expression in PDB osteoclasts of a range of proteins commonly found in inclusions in such diseases, namely: valosin-containing protein (VCP), ubiquitin, p62, phosphorylated tau, beta amyloid, the 20S proteasomal subunit alpha and the proteasomal subunit beta. Rather than use manual staining, we here report on the results obtained with a Bond Max autostainer which allows better between-patient comparison and higher sensitivity than manual staining.

Decalcified, wax embedded bone biopsies of 4 patients with PDB in which presence of inclusions was confirmed by ultrastructural analysis and of 5 non-PDB controls were used. Brain tissue from a patient with Alzheimer's disease and osteoclastoma tissue served as positive controls (for inclusion bodies and for non-pagetic osteoclasts respectively). Stained sections were analyzed by light microscopy and numbers of osteoclasts and staining intensity assessed semi-quantitatively. For VCP staining, which was strong in all cells, a quantitative method was used to analyse whether staining intensity was different between osteoclasts and other bone cell types and varied between PDB and non-PDB.

VCP, ubiquitin, p62 and the proteasomal subunits alpha and beta were overexpressed in osteoclasts in patients with PDB and often localised in aggregates in nucleus and cytoplasm. No staining was seen for beta amyloid and tau in osteoclasts in patients with PDB or in controls. These results confirm earlier observations for p62 and ubiquitin in PDB and extend knowledge of the expression of inclusion-associated proteins in PDB and osteoclasts in general. The high expression levels of inclusion-associated proteins in PDB osteoclasts suggests that accumulation of these proteins may play a role in the pathogenesis of this disease.

P24

LONG-TERM REMISSION OF PAGET'S DISEASE AFTER INDUCTION OF REMISSION WITH ORAL ALENDRONATE: A FIFTEEN-YEAR FOLLOW-UP STUDY.

K J Cukier, N J Harrison, K M Sanders, M A Kotowicz, G C Nicholson

The University of Melbourne, Department of Clinical and Biomedical Sciences: Barwon Health, Geelong, Victoria 3220, Australia

Aim: To determine long-term remission rates and predictors of relapse of Paget's disease in patients who achieved remission following initial treatment with oral alendronate.

Method: Nineteen patients with Paget's disease (mean baseline ALP 576 U/L) who received oral alendronate 40mg daily for 6 to 12 months during 1993-1994 while participating in a randomized placebo-controlled trial (Reid IR et al 1996 Am J Med 101:341-8) were followed long-term (median 135 months). Relapse was defined as ALP rising to >2.5 times nadir, or ALP >140 U/L, and/or symptomatic relapse with bone pain at a known pagetic site. Patients were followed until March 2009 (n=7), death (n=7) or loss of contact (n=5).

Results: Eight patients (42%) had not relapsed at median follow-up time of 41 months (range 18-178 months). Three of these who had not relapsed at 178, 144 and 72 months had baseline ALPs of 339, 1282 and 187 U/L, respectively. Eleven patients (58%) who relapsed did so at a median time of 30 months (range 15-172 months). Of patients who had been treated with alendronate for 6 months 7 of 10 (70%) relapsed, whereas 4 of 9 (44%) of those treated for 9-12 (median 11) months relapsed (p=0.370). Neither pre-treatment ALP nor nadir ALP predicted long term remission. All patients who relapsed had subsequent relapses.

Conclusions: After induction of remission of Paget's disease with oral alendronate 40mg daily for 6-12 months, 42% of patients experienced long-term remission lasting up to 15 years. In this relatively small group it was not possible to identify predictors of long-term outcome, although relapse was associated with subsequent relapse

and longer duration of initial alendronate treatment (or total dose) may be associated with longer remission.

P25

PAGET'S DISEASE OF BONE: ANALYSIS OF 134 CASES IN A SMALL ISLAND OF THE SOUTH OF BRAZIL

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Rheumatology Division of Santa Catarina Federal University, Brazil

Purpose: The aim of this study was to investigate the epidemiology, clinical features and responses to therapy in patients with Paget's disease of Bone (PDB) from the island of Florianópolis in southern Brazil.

Methods: This was an observational study based on a chart review of 134 patients. Association and correlation tests between symptoms, laboratory findings, skeletal scintigraphy and x-ray were done. The results of different treatments were analyzed.

Results and Discussion: The mean age was 63.6 years, 67 % were women, and 91 % were Caucasian. Total alkaline phosphatase (AP) and bone AP levels were abnormal in 70.6% and 69.4% respectively, with mean total AP of 548mg/dl and bone fraction of 341 mg/dl. Polyostotic disease was found in 75% of the cases, bone pain in 77.9%, bone deformities in 15.9%, while 19.5% were asymptomatic. Bone scintigraphy was abnormal in 99%. Other features included deafness in 8.2%, bone fractures in 3%, hydrocephalus in 2.2%, and cauda equina syndrome in 0.7%. Polyostotic disease was associated with higher values of AP and with skull disease.

Interestingly, a positive family history was reported in only 8.2%. This population includes many European migrants from the Azores and genetic studies are planned. Treatment with zoledronic acid achieved the best clinical responses, with only 2.9% failing to respond adequately.

Conclusion: Paget's disease of bone is frequent in different regions of the world, as found in this region in south Brazil. Zoledronic acid was very effective and the treatment of choice in these patients.

POSTERS

Monday and Tuesday

Posters presented by PhD students:

Fredrik Agholme (Linköping, Sweden):
Drug release systems for local treatment of bone fractures

Hermann Agis (Vienna, Austria):
Cellular mechanisms of guided bone regeneration: The impact of platelets and biomaterials in vitro

Elisa Benasciutti (Milan, Italy):
Mouse genetics models reveal MHC class II transactivator as a novel regulator of osteoclastogenesis and bone homeostasis co-opted from adaptive immunity

Cynthia Chang (Oxford, UK):
Mechanotransduction and differentiation in distraction osteogenesis

Hannah Cornell (Oxford, UK):
Factors contributing to chondroplasia in degenerate rotator cuff disease

Emmanuel Coste (Edinburgh, UK):
Inhibitors of TRAF signalling pathways as anti-inflammatory and anti-resorptive drugs

Aimee Duan (Oxford, UK):
Physiological and biological mechanisms of bisphosphonates action

Tania Fernandes (Melbourne, Australia):
Osteoblastogenesis from human umbilical cord-derived mesenchymal stem cells - Biology on novel implantable scaffolds

Jenna Fong (Montreal, Canada):
Inhibition of osteoblast differentiation by breast cancer cells promotes tumor cell attachment to bone cells

El Mustapha Haddouti (Bonn, Germany):
Mesenchymal stem cells potential in tissue engineering for bone regeneration

Behzad Javaheri (London, UK):
The role of Wnt signaling in mediating bone cell's response to mechanical strain

Xuan Jiang (Nanjing Jiangsu, China):
Sclerostin mediates bone response to mechanical unloading via antagonizing Wnt B-catenin signaling

Robert Little (Sheffield, UK):
The calcium selective channels TRPV5 and TRPV6 in osteoblasts and osteoclasts

Hongbin Liu (Kansas City, USA):
Hedgehog signaling pathway activates BMP2 and Runx2 expression in osteoblast by deletion of Stathmin1

Katie Marchbank (London, UK):
The role of Nbr1 in bone remodelling

Silvia Marino (Turin, Italy):
Pharmacological treatment of bone fracture healing

Helen McCarthy (Oswestry, UK):
Wnt signalling in osteoblastic cells

David Mellis (Aberdeen, UK):
RANK mutations associated with early onset forms of Paget's disease and osteopetrosis

Alaa Metwalli (London, UK):
An *in vivo* study of the pathways involved in the bone's response to mechanical loading

Martiene Moester (Leiden, Netherlands):
Modulation of sclerostin expression in osteoporosis

Brian Nicholls (London, UK):
The role of AKT in mediating the adaptive response of osteoblasts to mechanical strain

Suruchi Pacharne (Sheffield, UK):
Roles receptor activity modifying proteins in the skeleton

Maria Guadalupe Pippa (Sao Paolo, Brazil):
Clinical and laboratorial factors related to high bone mineral density in post menopausal women

Roberta Scianaro (Rome, Italy):
Role of the immune system in bone resorption

Amir-Shaya Sharili (London, UK):
The role of the transcription factor Snail2 in bone cancer and repair

Maria Tsoumpra (Oxford, UK):
The interaction of nitrogen containing bisphosphonate drugs with mevalonate pathway enzymes

POSTERS

Wednesday

Bisphosphonates Birthday Party

EFFECT OF ONCE-YEARLY ZOLEDRONIC ACID IN MEN AFTER RECENT HIP FRACTURE: RESULTS FROM HORIZON RECURRENT FRACTURE TRIAL
S Boonen*[1], J Magaziner[2], KW Lyles[3], C Colon-Emeric[3], JD Adachi[4], C Bucci-Rechtweg[5], P Mesenbrink[5]
[1]University of Leuven, Leuven, Belgium;[2]University of Maryland, Baltimore, US;[3]Duke University and VA Medical Centers, Durham, NC, US;[4]McMaster University, Hamilton, Ontario, Canada; [5]Novartis Pharmaceuticals, East Hanover, US

A ONCE-YEARLY TREATMENT WITH ZOLEDRONIC ACID CONTINUES TO BE EFFECTIVE IN OLDER AGE
I Reid[1], S Boonen*[2], D Black[3], C Colon-Emeric[4], KW Lyles[4,5], R Eastell[6], J Magaziner[7], P Mesenbrink[8], EF Eriksen[9]
[1]University of Auckland, New Zealand;[2]University of Leuven, Belgium;[3]UCSF, San Francisco, US;[4]Duke University and VA Medical Centers, Durham, NC, US;[5]Carolina's Center for Medical Excellence, Cary, NC;[6]University of Sheffield, UK;[7]University of Maryland, Baltimore, US;[8]Novartis Pharmaceuticals, East Hanover, US;[9]Oslo University Hospital, Oslo.

EFFECT OF I.V. ZOLEDRONIC ACID ON LUMBAR SPINE BONE MINERAL DENSITY COMPARED TO ORAL RISEDRONATE IN SUBGROUPS OF PATIENTS RECEIVING GLUCOCORTICOID THERAPY
C Roux*[1], D Reid[2], J Devogelaer[3], K Saag[4], J Reginster[5], P Papanastasiou[6], P Mesenbrink[7], P Sambrook[8]
[1]Paris-Descartes University, Paris, France,[2]University of Aberdeen, Aberdeen, United Kingdom,[3]Universite Catholique de Louvain, Brussels, Belgium,[4]University of Alabama at Birmingham, Birmingham, AL, USA,[5]University of Leige, Liege, Belgium,[6]Novartis Pharma AG, Basel, Switzerland,[7]Novartis Pharmaceutical Corp., East Hanover, NJ, USA,[8]University of Sydney, Sydney, Australia.

ONCE-YEARLY ZOLEDRONIC ACID INREASES THE PROXIMAL FEMUR STRENGTH AS ASSESSED BY FINITE ELEMENT ANALYSIS OF QCT SCANS
R Eastell*[1], L Yang[1], AV Sycheva[1], L Palermo[2], DM Black[2]
[1]University of Sheffield, Sheffield, United Kingdom, [2]University of California, San Francisco, United States

EFFECT OF ONCE-YEARLY ZOLEDRONIC ACID 5 MG ON 'SUPER SIX' NONVERTEBRAL FRACTURES
DM Black[1], R Eastell[2], F Cosman[3], Z Man[4], C Bucci-Rechtweg[5], P Mesenbrink[5], on behalf of the HORIZON-PFT investigators
[1]University of California, San Francisco, USA; [2]University of Sheffield, Sheffield, UK; [3]Helen Hayes Hospital, West Haverstraw, New York, USA; [4]Centro TIEMPO, Buenos Aires, Argentina;[5]Novartis Pharmaceuticals Corporation, New Jersey, USA

EFFICACY AND SAFETY OF ZOLEDRONIC ACID IN THE PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN WITH OSTEOPENIA: THE HORIZON PREVENTION STUDY
MR McClung*[1], P Miller P[2], C Recknor[3], ME Ruzycky[4], C Bucci-Rechtweg[4], S Yu[4], CL Benhamou[5]
[1]Oregon Osteoporosis Center, Portland, OR; [2]Colorado Center for Bone Research, Lakewood, CO; [3]United Osteoporosis Centers (UOC), Gainesville, FL; [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [5]IPROSA-Regional Hospital of Orleans, Orleans, France

COMPARABLE TRABECULAR ARCHITECTURE IN OSTEOPOROTIC WOMEN TREATED WITH ONCE-A-MONTH (150 MG) AND DAILY (5 MG) RISEDRONATE: 3D MICRO-CT ANALYSIS OF BIOPSIES FROM AN ACTIVE-CONTROLLED STUDY
B Borah*, J Nurre, P Chmielewski, T Dufresne, L Wagner
Procter & Gamble Pharmaceuticals, Cincinnati, OH, USA

OFFSET OF EFFECT ON BONE RESORPTION AFTER 7 YEARS OF RISEDRONATE THERAPY
RA Hannon[1] , CR Purple[2], AB Klemes[2], GA Cline[2], RE Eastell[1]
[1]University of Sheffield, Sheffield, UK; [2]Procter & Gamble Pharmaceuticals, Mason OH, USA

RISEDRONATE REDUCES INTRACORTICAL POROSITY IN WOMEN WITH OSTEOPOROSIS

B Borah[1], T Dufresne[1], J Nurre[1], P Chmielewski[1], R Phipps[4], L Wagner[1], M Bouxsein[2], E Seeman[3]
[1]Procter & Gamble Pharmaceuticals, Mason, Ohio, USA; [2]Ortho Biomechanics Lab, Harvard Medical School, Boston, MA, USA; [3]Austin Health, University of Melbourne, Melbourne, Australia; [4]Maine Institute for Human Genetics & Health, Brewer, ME, USA

THE DIFFERENTIAL DISTRIBUTION IN VIVO OF FLUORESCENTLY-LABELED BISPHOSPHONATE ANALOGUES WITH DIFFERENT MINERAL AFFINITY TO BONE SURFACES

A Boyde[1], MW Lundy[2]; FP Coxon[3]; CE McKenna[4]; A Roelofs[3]; J Bala[4]; MJ Rogers[3]; K Blazewska[4]; RGG Russell[5]; FH Ebetino[2]
[1]Queen Mary University of London, London, UK; [2]Procter and Gamble Pharmaceuticals, Mason, OH, USA; [3]University of Aberdeen, Aberdeen, UK; [4]University of Southern California, Los Angeles, CA, USA; [5]The Botnar Research Centre, Nuffield Department of Orthopaedic Surgery, University of Oxford, UK

EVIDENCE FOR THE INVOLVEMENT OF THE THREONINE 201 SIDE-CHAIN IN THE INTERACTION OF NITROGEN-CONTAINING BISPHOSPHONATES WITH FARNESYL PYROPHOSPHATE SYNTHASE

AAA Kwaasi*[1], ES Pilka[2], A Evdokimov[3], BL Barnett[4], FH Ebetino[3], RGG Russell[1], KL Kavanagh[5], U Oppermann[2], JE Dunford[1]
[1]Nuffield Department of Orthopaedic Surgery, Oxford University, United Kingdom; [2]Structural Genomics Consortium, Oxford University, Oxford, United Kingdom; [3]Procter & Gamble Pharmaceuticals, Cincinnati, United States; [4]University of Cincinnati, United States; [5]University of Texas at Austin, Austin, United States

THE INFLUENCE OF TYROSINE 204 OF FARNESYL PYROPHOSPHATE SYNTHASE ON THE MECHANISM OF INHIBITION BY NITROGEN-CONTAINING BISPHOSPHONATES

MK Tsoumpra[1,2], BL Barnett[3], A Kwaasi[1], FH Ebetino[4], U Oppermann[2] , RGG Russell[1], JE Dunford[1,2]
[1]Institute of Musculoskeletal Sciences, Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, University of Oxford, UK, [2]Structural Genomics Consortium, University of Oxford UK, [3]Dept. Chemistry, University of Cincinnati, OH, USA, [4]Procter & Gamble Pharmaceuticals, Cincinnati, OH, USA.

INVITED SPEAKERS

SHORT BIOGRAPHIES

Lynda Bonewald

Dr Bonewald received her PhD Degree in 1984 from the Medical Univ. of S. Carolina in Immunology and Microbiology and performed her postdoctoral fellowship with Dr. Makio Ogawa in the area of hemopoeitic stem cell growth factors. She joined Dr. Gregory Mundy's group at the Univ. of Texas Health Science Center in San Antonio in 1986. In 2001 she became Director of the Bone Biology Research Program at the Univ. of Missouri at Kansas City and is Director of the UMKC Center in the Study of Mineralized Tissues. Dr. Bonewald has worked in the area of transforming growth factor β and in the lipoxygenases, but is probably best known for her research in osteocyte biology. She is an Associate Editor for *Journal for Bone and Mineral Research* and serves on the editorial boards for the *Journal for Biomolecular Techniques, Bone,* and *Experimental Biology and Medicine*. She is program co-organizer for ASBMR 2009 and is ASBMR Treasurer-Elect.

Matthew Brown

Matt Brown is a clinician-scientist who trained initially in medicine and rheumatology in Sydney, Australia before moving in 1994 to Oxford, England. Working first at the Wellcome Trust Centre for Human Genetics and then the Botnar Research Centre (University of Oxford Institute of Musculoskeletal Sciences), he pursued gene-mapping and genetic epidemiology studies in musculoskeletal diseases, including ankylosing spondylitis, rheumatoid arthritis, chondrocalcinosis and osteoporosis. He was appointed Professor of Musculoskeletal Sciences at University of Oxford in 2004 and was Deputy Director of the Botnar Research Centre from 2003-5. In 2005 Matt returned to Australia, taking a chair of Immunogenetics at University of Queensland, based at the Diamantina Institute in Brisbane. There he continues to work in genetics of common diseases, with a particular focus on bone and joint diseases, in humans and mice.

Henry Bryant

Henry U. Bryant, Ph.D., is the Chief Scientific Officer of the Musculoskeletal Drug Hunting Team within the Lilly Research Laboratories, Eli Lilly and Co., in Indianapolis, Indiana. His initial training and licensure was as a pharmacist in 1981. He then went on to receive his Ph.D. in pharmacology from Purdue University (W. Lafayette, Indiana) in 1986 for his work on endogenours opioid phamracology. He continued his basic research training as a National Research Council post-doctoral fellow at the Walter Reed Army Institute of Research (Washington, D.C.) with a primary focus on neuroendocrine regulation of immunity. In 1988 he joined the Lilly Research Laboratories and developed research programs focused on employing pharmacological strategies to understand diseases of the bone and connective tissue, with the ultimate goal of developing novel therapeutic agents for pathological conditions associated with the aging process. He co-authored the first paper describing the selective estrogen receptor, or SERM, profile of raloxifene in pre-clinical models and maintains an active laboratory effort in this area. His research group conducted the pre-clinical drug discovery research that has led to the registration of two marketed compounds for osteoporosis (Evista and Forteo/Forsteo), as well as moving additional molecules into clinical trials for osteoporosis, frailty and various women's and men's health-related indications (i.e. uterine fibroids, endometriosis, breast cancer, benign prostatic hypertrophy). Dr. Bryant is the author of over 100 manuscripts in peer-reviewed journals along with 15 book chapters and monographs and has spoken at numerous international scientific conferences on his research efforts. He is a member of the American Society for Pharmacology and Experimental Therapeutics (ASPET), the American Society for Bone and Mineral Research (ASBMR), the Endocrine Society, the Society for Neuroscience and the Indiana Academy of Science and is a Distinguised Alumni of the Purdue University School of Pharmacy. He has served as a member of the Drugs of Abuse and AIDS study section of the NIH, and is a reviewer for a number of pharmacology and physiology based journals.

Tim Cundy

Tim Cundy trained in medicine at the Cambridge University and Kings College Hospital Medical School, London, and was later a research fellow in Oxford. At various stages he trained under Victor Parsons, Nick Woodhouse, Ronnie Hamdy, John Kanis and Roger Smith, all of whom had keen interest in Paget's disease. Tim moved to the University of Auckland, New Zealand in 1988, where he remains involved with Paget's disease, both in clinical management and research. He was appointed to a personal chair in medicine in 2004.

Anna Daroszewska

Anna Daroszewska, MRCP, PhD, is Clinical Senior Lecturer in Rheumatology, University of Edinburgh, and Honorary Consultant with Lothian Health Board. Dr Daroszewska

graduated from the Medical Academy of Gdansk, Poland and moved to the UK, where she trained in rheumatology and general medicine. She developed a clinical and research interest in metabolic bone diseases and in particular Paget's disease of bone during postgraduate training with Prof Bill Fraser and Prof Rob Moots at the University of Liverpool. She obtained a MRC Clinical Research Training Fellowship to investigate the genetic basis of Paget's disease of bone and moved to the University of Aberdeen to work under the supervision of Prof Stuart Ralston. Since 2005 she has been working with Prof Stuart Ralston in the University of Edinburgh. Her research interests include the molecular genetics of Paget's disease of bone and development of models for metabolic bone diseases.

Patricia Ducy

Patricia Ducy, PhD, is currently an assistant professor in the Department of Pathology and Cell Biology 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. More recently, she and Dr. Karsenty showed that osteoblasts, the bone-forming cells, regulate energy metabolism by secreting a novel hormone, osteocalcin, and that gut-derived serotonin is a major regulator of bone mass accrual. Her research uses a combination of molecular biology, mouse genetics, and physiology to analyze the molecular mechanisms controlling bone cell differentiation and skeleton homeostasis.

Richard Eastell

Richard Eastell is Professor of Bone Metabolism at the University of Sheffield.

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 Director of the NIHR BRU in Bone Diseases, University of Sheffield, Northern General Hospital, Sheffield. He 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 also in 2004, the Society of Endocrinology Medal. He is on the editorial board of Osteoporosis International, Osteoporosis Review and an Associate Editor of Bone. He is the Past President of the European Calcified Tissue Society and Past Chairman of the National Osteoporosis Society.

Hal Ebetino

Frank H. Ebetino (Hal) received his PhD degree in Organic Chemistry at the University of Rochester, Rochester, NY. Dr. Ebetino has over 25 years of medicinal chemistry experience and has been a senior researcher and external research manager at Procter & Gamble Pharmaceuticals since 1984. He has been a Visiting Scholar at the University of Southern California, Los Angeles, since 2003. His research and publications span a variety of therapeutic areas including from Bone Metabolism, Arthritis, Obesity, Anti-infectives, and Cancer. He is most well known for his many years of research on the bisphosphonate class of bone active agents, and was part of the P&G team that discovered the therapeutic agent Actonel for osteoporosis. He continues to lead research on structure-activity relationships and bisphosphonate mechanisms of action. He serves on the scientific boards of the International Conference on Phosphorus Chemistry and the International Conference on Bisphosphonates in Davos, Switzerland.

James Edwards

James Edwards received his D.Phil. from Wadham College, University of Oxford studying with Prof. Nick Athanasou at the Botnar Research Centre, Institute of Musculoskeletal Sciences and later with Dr. Gregory Mundy at the University of Texas Health Science Center at San Antonio. He currently holds a faculty position at the Center for Bone Biology, Vanderbilt University, where he runs an active program investigating bone cell formation and function in normal and aging conditions. Over the past 14 years Dr. Edwards has pursued an interest in cellular pathology and bone biology within laboratories across the UK, Australia and America. Over this time he has won several awards, most recently the ASBMR Outstanding

Contribution to the Pathophysiology of Osteoporosis Award and AIMM John Haddad Young Investigator Award. His work encompasses numerous aspects of bone biology from the molecular mechanisms of bone cell interactions to advanced models of skeletal development, cancer-induced bone disease, fracture repair and most recently, age-related bone loss. His current studies focus on the sirtuin gene family as a common regulatory link between the aging process and bone loss, identifying a potential underlying mechanism in the onset and progression of osteoporosis.

Erik Fink Eriksen

Erik Fink Eriksen is Professor of Endocrinology at Oslo University since September 2008. His previous appointments include Global product Medical Director (Arthritis and Bone Therapeutic Area) at Novartis Pharmaceuticals, Basel, Switzerland (2005-2008). Global Medical Director, Eli Lilly & Co., Indianapolis, USA (2002–2005), Head and Consultant, Department of Endocrinology and Internal Medicine, Aarhus Amtssygehus (1995–2002), and Assoc. Professor, University of Aarhus (1995-2002). Dr Eriksen graduated with an MD from the University of Aarhus in 1980. Following the completion of his residency at Aarhus Kommunehospital and Aarhus Amstssygehus between 1980 and 1985, he joined the Department of Endocrinology and Internal Medicine, Mayo Clinic, USA as a Postdoctoral Fellow between 1985 and 1987. Completing a Clinical Fellowship in Internal Medicine in 1989, Dr Eriksen served as Senior Clinical Fellow at Aarhus University Hospital between 1989 and 1995. Concomitant with his clinical activities he led a bone research lab focusing on basic bone biology, calcium metabolism and histomorphometry. 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 bone and calcium-metabolic research in the areas of: genetics of osteoporosis, hormonal action on osteoblasts and osteoclasts, immuno-cytochemistry of bone, vitamin D metabolism, regulation of bone remodeling and osteocyte biology. Moreover, his group was involved in clinical trials with various osteoporosis therapies, and provided the histomorphometric analysis of the global risedronate and PTH (1-34) clinical trials. In addition to serving on a number of scientific societies and committees, Dr Eriksen sits on the Board of Directors of the International Society for Bone Morphometry.and is a member of the Committee of Scientific Advisors, International Osteoporosis Foundation (1998-). Previously he served as Chairman Advisory Board, Danish Osteoporosis Society (1994–2000), Chairman, Danish Bone and Tooth Society (1989–1993) and Board Member, Danish Endocrinology Society (1989–1993, Scientific Editor of the *European Journal Clinical Investigation* , Editorial Boards of *Bone*, *Journal of Bone and Mineral Research*, *Osteoporosis International* and *European Journal of Musculoskeletal Research*. He has authored 257 publications in peer-reviewed journals and 3 books.

Serge Ferrari

Dr Ferrari is currently Professor of osteoporosis genetics and medicine at the Geneva Faculty of Medicine, and Medical Associate at the Department of Rehabilitation and Geriatrics of the Geneva University Hospital, Switzerland. He serves on the teaching committee of the Geneva Faculty of Medicine and teaches internal medicine, pathophysiology and bone metabolism to pre-graduate students.

Dr Ferrari graduated from the Geneva University Faculty of Medicine in Switzerland in 1989, was Resident and Chief-Resident in Internal Medicine at the Geneva University Hospital, and then a post-doctoral fellow at Beth Israel Deaconess Medical Center in Boston (1997-2001), during which time he was appointed Instructor in Medicine at Harvard Medical School (2000).

He is president of the Swiss Bone and Mineral Society, founding member and on the board of directors of the International Society of Nutrigenetics and Nutrigenomics (ISNN), and member of the council of scientific advisors of the International Osteoporosis Foundation (IOF). Dr Ferrari is a member of the editorial board of *Journal of Bone and Mineral Research, Osteoporosis International* and *Bone,* and editor-in-chief of *BoneKEy,* an on-line journal and knowledge environment of the International Bone Mineral Society (IBMS) . He is the recipient of many international awards, as well as three-times winner of the clinical research award from the Swiss Bone and Mineral Society.

Dr Ferrari's current research interests include bone growth and fragility in childhood, genetics of osteoporosis, and the molecular mechanisms of PTH activity and bone remodeling. He has published more than 150 articles and book chapters in the bone field.

Nathalie Franchimont

Nathalie Franchimont, M.D., Ph.D. is the International Medical 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 tenure research scientist at the FNRS, the Belgian National Institute for Scientific Research. Her 3-year basic research training with Ernesto Canalis in Hartford, CT, USA, led to defense of her Ph.D. thesis at the University of Liège in 1998. As a rheumatology fellow in 1997 at Yale University, USA, she developed 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 numerous outstanding papers in the field of inflammatory cytokines and bone metabolism*. She has also been developing clinical research projects for patients presenting with secondary or post-menopausal osteoporosis, as well as osteonecrosis. She has been involved in teaching programs for students, general practitioners, and specialists concerning osteoporosis in her country and across Europe.

She is a member of the Royal Belgian Society of Rheumatology, the International Bone and Mineral Society, the European Calcified Tissue Society and the American Society for Bone and Mineral Research. She retains a position of "collaborator" at the University of Liège and still serves as a reviewer for several International Journals.

Francis Glorieux

Francis H. Glorieux received his M.D. from the University of Louvain in 1963 and his Ph.D. from McGill University in 1972. It is there that he developed his interest in heritable pediatric bone diseases. His recent work focused on the beneficial effects of bisphosphonates in severe forms of Osteogenesis Imperfecta (OI). His program is now the standard of care for this severe condition. In 1972 Dr. Glorieux received a Queen Elizabeth II Scientist Award from the Medical Research Council of Canada. He is the Founding Director of the Genetics Unit at the Shriners Hospital for Children in Montreal, and a Professor of Surgery, Pediatrics and Human Genetics at McGill University. Among the Awards he received are the Bartter Award of the ASBMR and the Elsevier Award of the IBMS. He also served as President of the IBMS (1995-1998). In 2004, he was made an Officer of the Order of Canada.

David Goltzman

David Goltzman is Professor in the Departments of Medicine and Physiology of McGill University, Director of the McGill Centre for Bone and Periodontal Research, and Senior Physician in the Endocrine Division of the McGill University Health Centre.

His research has focused on the hormonal regulation of calcium and skeletal homeostasis, and he has made many important contributions to our knowledge of parathyroid hormone(PTH), PTH related peptide and vitamin D, which have had major impact on our understanding of a variety of metabolic bone diseases. He is also co-principal investigator of the Canadian Multicentre Osteoporosis Study(CaMos). Dr Goltzman has received various honours and awards, including the Aurbach Award of the US Endocrine Society and is a past President of the American Society for Bone and Mineral Research.

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

Aymen Idris is a pharmacologist and a senior research fellow at the University of Edinburgh (Scotland, UK). The focus of his research has been the design and development of novel therapeutic agents for the treatment of bone diseases. His PhD thesis yielded a number of patents for novel anti-resorptive and anti-rheumatic agents that target and prevent RANKL-dependent signalling. One of his particular areas of interest is the role of cannabinoids on bone metabolism. His work in this area has attracted great interest and was published in the reputable journal "Nature Medicine". His recent research has revealed the effects of cannabinoids on adipocyte differentiation and their role in age-related bone loss. The work of Dr Idris is funded by the Arthritis Research Campaign, the Scottish Enterprise and the Moray Endowments Research Trust. Dr Idris is a recipient of a number of Young Investigator Awards and the ECTS/AMGEN Bone Biology Fellowship (2006).

Morten Karsdal

Morten A. Karsdal, MSc, PhD, Professor, achieved his master of biotechnical engineering at the "Technical University of Denmark" in 1998. He achieved his PhD at the "University of Southern Denmark" 2004, with special focus on the cell and molecular biology of bone. Dr. Karsdal is Professor in "Molecular Medicine" at the "University of Southern Denmark" and is presently the Head of R&D at Nordic Bioscience. Dr. Karsdal has previously had various research positions at smaller biotech companies in Denmark. Morten Karsdal has more than 75 pier reviewed publications within the bone and cartilage field, and he has received research awards at more conferences, including the ECTS, ASBMR, OARSI and NYAS meetings.

One of Dr Karsdal's key research interests is the development of new biological models and biochemical assays for understanding of pathogenesis of diseases involving extensive extracellular matrix remodeling. This research is mainly focused on the identification of protein degradation products, neo-epitopes, that may be used for diagnostic, prognostic and efficacy of intervention purposes. In addition, Dr Karsdal is presently involved in investigating a potential anabolic signaling from osteoclasts to osteoblasts and the role of the chloride channel ClC-7 in osteoclasts. Another of his main interests is the interaction between bone and cartilage in the pathogenesis of osteoarthritis.

Gerard Karsenty

Dr. Karsenty is currently the Paul A. Marks Professor and Chairman of the Department of Genetics & Development at Columbia University (New York, NY). He received his MD/PhD degree from the University of Paris and was a faculty at the M.D. Anderson Cancer Center and at Baylor College of Medicine in Houston, TX. Dr. Karsenty's research interests include the transcriptional control of osteoblast differentiation and the genetic bases of skeleton physiology. His laboratory has identify Runx2 as the master gene of osteoblast differentiation and ATF4 as a major regulator of osteoblast function. Dr. Karsenty also showed that the adipocyte-derived hormone leptin is a powerful central regulator of bone mass using the sympathetic nervous system as peripheral effector and that in turn osteoblasts regulate energy metablism via secretion of osteocalcin. More recently, he identifed gut-derived serotonin as a negative regulator of bone mass accrual whose production is inhibited by Lrp5.

Sundeep Khosla

Dr. Sundeep Khosla is the Dr. Francis Chucker and Nathan Landow Research Professor at the College of Medicine, Mayo Clinic. He received his A.B. from Harvard College and his M.D. from Harvard Medical School. He was subsequently a resident in Internal Medicine and a fellow in Endocrinology at the Massachusetts General Hospital. In 1988 he moved to Mayo, where his research has focused on mechanisms of age-related bone loss. Dr. Khosla has been appointed to the Council of the National Institute on Aging and has received numerous awards and honors for his work, including the Frederic C. Bartter Award from the ASBMR, the Innovation Award from the NOF, and election to the ASCI and AAP. He has been elected President of the ASBMR for 2010-2011.

Michaela Kneissel

Senior Research Investigator II / Novartis Leading Scientist, Novartis Institute for BioMedical Research, Musculoskeletal Diseases, Basel, Switzerland

Michaela Kneissel leads the Early Bone Research Group 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. In recent years her research interest was centered on the bone formation inhibitor SOST and osteocyte biology. She is member of some decision making committees at the Novartis Institute for Biomedical Research, has published various papers on bone biology and currently serves on the editorial board of *Calcified Tissue International*.

Paul Kostenuik

Paul Kostenuik graduated with a B.Sc. in Kinesiology from the University of Waterloo, in Ontario Canada. He completed his Ph.D. in Medical Sciences at McMaster University in Hamilton Ontario, where he studied the pathophysiology of bone metastasis under the mentorship of Bill Orr and Gurmit Singh. Paul's first post-doctoral fellowship was done at the La Jolla Institute for Experimental Medicine. He then worked as a post-doc at the University of California San Francisco with Dan Bikle and Bernard Halloran, where he studied the effects of mechanical loading and unloading on bone. After UCSF he moved to Boston University, where he worked with Tom Einhorn and Lou Gerstenfeld investigating the molecular mechanisms of fracture repair. Dr. Kostenuik joined Amgen in 1999 as a Research Scientist to work on the preclinical development of OPG and its successor, denosumab. He is now Scientific Director in Metabolic Disorders Research, where he leads a team of scientists and research associates working on the preclinical

development of therapeutics for the treatment and prevention of bone loss.

David Little

Children's Orthopaedic Surgeon and Head, Orthopaedic Research and Biotechnology, Department of Orthopaedics, Associate Professor of Paediatrics and Child Health at the University of Sydney in Australia.

Interests: Bone Repair; Limb Lengthening and Reconstruction; Paediatric Hip Surgery; Perthes Disease and Osteonecrosis

Professor Little graduated MBBS from the University of Sydney in 1986. He received his FRACS(Orth) in 1995 and undertook further training at the Shriners Hospital for Children in Portland, OR, USA and Texas Scottish Rite Hospital for Children in Dallas TX, USA.

Professor Little is a clinician-scientist in Orthopaedics. In 1999 he opened a basic research group with a focus on bone repair and regeneration. This resulted in completion of his PhD in distraction osteogenesis in 2004. Professor Little was selected as the 2002 ABC Travelling Fellow. In 2005 he won the Robert N Hensinger Basic Science Paper Award for the Outstanding Paper at Paediatric Orthopaedic Society of North America.

Professor Little has over 50 publications in the orthopaedic literature on bone repair as well as clinically related topics in Paediatric Orthopaedics. He remains in active clinical practice as a Senior Staff Specialist specialising in hip surgery and trauma, as well as continuing his research interest as Head of Orthopaedic Research and Biotechnology.

Ken Lyles

Kenneth W. Lyles, MD, is Professor of Medicine, Vice Chair for Clinical Research, and Director of Medicine Site-Based Research at Duke University Medical Center in Durham, North Carolina. He also works as a staff physician in the Geriatric Research, Education, and Clinical Center at the Durham VA Medical Center and is Clinical Coordinator at The Carolinas Center for Medical Excellence in Cary, North Carolina. Dr. Lyles earned his medical degree from the Medical College of Virginia in Richmond and completed his internship and residency in Medicine at the Medical College of Virginia Hospitals. He subsequently completed a fellowship in Endocrinology and Metabolism at Duke University Medical Center and a fellowship in Geriatrics and Gerontology at the Durham VA Medical Center and Duke University Medical Center.

Dr. Lyles is a certified by the American Board of Internal Medicine in Endocrinology and Metabolism with Added Qualifications in Geriatric Medicine. He is a Fellow of the American College of Physicians, American Geriatrics Society, and the Gerontological Society of America and a member of a number of professional societies. Dr. Lyles is on the editorial boards of *Osteoporosis International*, *The Journal of Gerontology: Medical Sciences*, *The American Journal of Geriatric Pharmacotherapy*, and *Journal of the American Geriatrics Society*. His current research interests include hip and vertebral fractures, age-associated osteoporosis, and glucocorticoid-induced osteoporosis, and he has authored or coauthored more than 100 articles and book chapters.

T John (Jack) Martin

T.J. Martin is Emeritus Professor of Medicine, University of Melbourne and John Holt Fellow, St Vincent's Institute of Medical Research. After being Professor of Chemical Pathology at the University of Sheffield (UK) from 1974 until 1977, he was Professor and Chairman of the University of Melbourne Department of Medicine until 1999. He was Director of St Vincent's Institute of Medical Research from 1988 – 2002. His research has been in bone cell biology, the mechanisms of action of hormones that influence bone and calcium metabolism, intercellular communication in bone and the differentiation of bone cells, and the effects of cancers upon the skeleton. A Fellow of the Royal Society and of the Australian Academy of Science, he has been President of the International Bone and Mineral Society and Vice President of the international Cancer and Bone Society, and serves as Associate Editor or Board Member of a number of journals. Among awards were the Dale Medal in 1992 (UK), the Chemofux Research Prize in 1988 (Vienna), the William F Neuman Award in 1994 (USA), Pieter Gaillard Award of IBMS in 2003, the Ramaciotti Award in 2004, and the Gideon A Rodan Award for Mentorship in 2007 He has published more than 600 scientific articles and reviews and 6 books.

Simon Mays

Having previously done an undergraduate degree in chemistry, I received my PhD in archaeology from the University of Southampton in 1987, my thesis allowing me to combine my twin interests in marxist social theory and human skeletal biology. I then spent a year on a project which involved teaching archaeology to school children. I started my current post, human skeletal biologist for English Heritage, in 1988. This involves responsibility for developing and implementing EH policy regarding human skeletons excavated from archaeological sites, and overseeing scientific work on human remains funded by English Heritage. I am based at the English Heritage Centre for Archaeology in Portsmouth. I am a visiting lecturer at the Archaeology Department University of Southampton and I also teach on an occasional basis in

the Archaeology Department at the University of Edinburgh. My research interests span all areas of research on archaeological human skeletal remains.

Eugene McCloskey

Eugene McCloskey is Senior Lecturer in Metabolic Bone Diseases in the Academic Unit of Bone Metabolism and WHO Collaborating Centre for Metabolic Bone Diseases at the University of Sheffield. Working in the field of calcium and bone disorders since 1986, early interests included osteolytic bone disease leading to the established role for bisphosphonates in multiple myeloma and breast cancer. He has been principal investigator in many clinical studies and published over 120 peer-reviewed publications, book chapters and reviews. He is an acknowledged authority in the fields of vertebral fracture definition, osteoporosis epidemiology, fracture risk and bone health in cancer. He contributed to the development of the FRAX tool for fracture risk assessment and the subsequent guideline from the National Osteoporosis Guideline Group. He is on a number of editorial boards and is a member of committees within the IOF, the Bone Research Society Committee and the ASBMR.

Joan McGowan

Joan A. McGowan, Ph.D., is the Director of the Division of Musculoskeletal Diseases at the National Institute of Arthritis and Musculoskeletal and Skin Diseases. She received her Masters in Nutritional Sciences at Cornell University and a Ph.D. in Biomedical Science at Brown University. Before joining NIH, Dr. McGowan was a faculty member at the Harvard Medical School. Dr. McGowan has been very active in osteoporosis and women's health activities at NIH, including serving as a Project Officer in the Women's Health Initiative. She co-chairs the Federal Working Group on Bone Diseases whose members represent all of the U.S. federal agencies with activities in osteoporosis and related bone disease. She was the NIH organizer of a Consensus Development Conference on Optimum Calcium Intake in 1994 and one on Osteoporosis held in March, 2000. She served as the Senior Scientific Editor of the Surgeon General's Report on Osteoporosis and Bone Health published in 2004.

Edward Nemeth

Edward F. Nemeth received a B.A. in psychology and chemistry from Lawrence University, a M.A. in psychology from Princeton University and a Ph.D. in pharmacology from Yale University. He was an assistant professor in the Department of Physiology and Biophysics at Case Western Reserve University School of Medicine and the Chief Scientific Officer at NPS Pharmaceuticals. He is the founder of MetisMedica and he co-directs the drug discovery course in the Department of Pharmaceutical Sciences at the University of Toronto. Dr. Nemeth's primary research interests are the pharmacology of G protein-coupled receptors and the physiology of bone and mineral metabolism. He discovered the first molecules that act on the calcium receptor and coined the terms "calcimimetic" and "calcilytic." The first drug to emerge from his work is the calcimimetic cinacalcet used to treat hyperparathyroidism.

Udo Oppermann

Udo Oppermann leads the Metabolic Enzymes group within the Structural Genomics Consortium at the University of Oxford Nuffield Department of Clinical Medicine. Research activities are aimed at the production, purification, functional characterization and structure determination of human metabolic enzymes of medical interest. Previous experiences relevant to the research area are: functional and structural characterization of oxidoreductases, analysis of relevant biochemical pathways (hormone, lipid, and drug metabolism) and pharmacology/enzymology of dehydrogenase drug targets.

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 basic and clinical research in disorders of calcium and bone metabolism.

Vishwas Paralkar

Dr Paralkar is Director of Exploratory Biologics at in the Department of Cardiovascular and Metabolic Diseases at Pfizer Global Research and Development. He has been with Pfizer since 1995 and before that was at the National Institutes of Health.

Joanna Price

Joanna Price graduated as a veterinary surgeon from Bristol University in 1983 then spent a number of years in first opinion clinical practice before undertaking her PhD training with Professor Graham Russell on the biology of deer antler regeneration. After two years working as a Wellcome Trust Post-Doctoral Fellow on bone's

adaptation to mechanical loading in Professor Lance Lanyon's laboratory, she was awarded a Wellcome Trust Career Development Fellowship to continue with her research on antler regeneration under the mentorship of Professor Mike Horton at University College London. She returned to the Royal Veterinary College in 2000 as a faculty member, was appointed Professor of Veterinary Anatomy in 2005 and was Chair of the College's Basic Science Department until 2008. Working in collaboration with Lance Lanyon, her current research focuses on mechanically-related functional adaptation in bone, in particular interactions between the oestrogen receptor and other signalling pathways. She also has a long-standing clinical research interest in the pathogenesis and prevention of musculoskeletal injuries in horses.

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. He is academic director of Edinburgh Clinical Trials Unit; is an Honorary Consultant Rheumatologist with NHS Lothian 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, the role of the endocannabinoid system in bone and the pathogenesis and management of cancer-associated bone disease. He has previously served on the Oliver Bird Committee of the Nuffield Foundation, the Heberden Committee of the British Society of Rheumatology, the Molecular and Cellular Medicine Board of the MRC, the Physiological Medicine and Infections Board of the MRC, the Physiology and Pharmacology panel of the Wellcome Trust; the Committee for Safety of Medicines and the Research Subcommittee of the Arthritis Research Campaign. He acts as scientific advisor to the National Association for Relief of Paget's Disease and the Paget Foundation. He is a past president of the Bone and Tooth Society of the UK, and was President of the European Calcified Tissues Society (ECTS) between 1998-2005. He is currently joint editor-in-chief of Calcified Tissue International, associate editor of Bone and chair of the Professional Practice Committee of the ECTS. He is chair of the Rheumatology and Immunology expert advisory group of the Medicines and Healthcare products Regulatory authority (MHRA) and a member of the MHRA expert advisory group on medicines for women's health and on clinical trials.

Ian Reid

Ian Reid MD is Professor of Medicine and Endocrinology at the University of Auckland, New Zealand, where he is Deputy Dean of the Faculty of Medical and Health Sciences. His research interests include the causes and treatment of osteoporosis & Paget's disease. He is immediate a past president of the International Bone and Mineral Society and of the Australia and New Zealand Bone and Mineral Society, is Secretary of the Asian Pacific Osteoporosis Foundation, and is a Fellow of the Royal Society of New Zealand.

Sevgi Rodan

Sevgi Rodan started her career in bone biology as a postdoctoral fellow at the University of Connecticut Health Center working with Gideon Rodan, studying signaling by PTH and calcitonin in isolated calvarial bone cells, and establishing clonal cell lines from rat osteosarcoma with osteoblastic phenotype. After moving to Merck & Co., in an effort to identify novel drug targets for prevention of bone loss, she focused her research in osteoclasts. In the early 1990s, she led an effort to investigate the role of $\alpha v\beta 3$ integrin, a highly abundant cell surface attachment protein expressed in osteoclasts, in bone resorption. In the mid 1990s, she and her colleagues initiated research to identify potent and selective inhibitors of cathepsin K, a predominant cysteine protease in osteoclasts, capable of degrading triple helical region of type I collagen. These novel inhibitors of bone loss are being developed for treatment of osteoporosis. She is currently adjunct professor at the University of Pennsylvania.

Michael Rogers

Mike Rogers studied Biochemistry in the Department of Molecular Biology & Biotechnology at the University of Sheffield and received his doctorate from the same University in 1993. He was awarded the JG Graves

Medical Research Fellowship to continue his studies on bisphosphonate pharmacology, then moved in 1997 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 in recognition of his major contribution to discovering the molecular mode of action of bisphosphonate drugs, and is currently the leader of the multidisciplinary Bone & Musculoskeletal Research Programme at the University of Aberdeen. His own research is focused on the molecular pharmacology of bone-active agents, the role of the mevalonate pathway in bone metabolism, and small GTPases and other signalling molecules involved in regulating osteoclast activity.

Professor Rogers is a member of the Board of Directors of the International Bone & Mineral Society, and a member of the Grants Committee of the European Calcified Tissue Society. He is also a member of the editorial board of *Bone* and *Calcified Tissue International*, and was the first recipient of the *Iain T Boyle Award* by the European Calcified Tissue Society, and the *Herbert A. Fleisch Award* by the International Bone & Mineral Society. His work has been funded from various sources including the Arthritis Research Campaign, Cancer Research UK and the Wellcome Trust, and he maintains strong links with the pharmaceutical industry.

G David Roodman

G David Roodman received a medical degree from the University of Kentucky College of Medicine and a doctorate in biochemistry from the University of Kentucky. His postdoctoral training included an internship in internal medicine at the University of Kentucky, as well as a residency in medicine and a hematology fellowship at the University of Minnesota. Dr. Roodman currently serves as Director of the Myeloma Program at the University of Pittsburgh Cancer Institute and Vice Chair for Research in the University of Pittsburgh School of Medicine's Department of Medicine.

An American Board of Internal Medicine Diplomate in internal medicine and hematology, and a Diplomate of the National Board of Medical Examiners, Dr. Roodman holds membership in numerous professional societies and holds positions of prominence with several advisory and regulatory bodies, including Chair of the Paget Foundation. Among Dr. Roodman's many awards are the Louis V. Avioli Founders Award for Basic Research in Bone (2007) and the John B. Johnson Award for Research in Paget's Disease (2002).

Dr Roodman is well-published in the peer-reviewed literature and is on the editorial boards of several journals, including *Experimental Biology and Medicine* and *Journal of Clinical Investigation.* Additionally, he is Associate Editor of *Journal of Bone and Mineral Research*. Dr. Roodman's research focuses on the cellular and molecular events that control the formation and activity of osteoclasts in normal and pathologic states, and he is a highly sought lecturer on these topics. He holds two investigator-initiated National Institutes of Health grants and heads a Program Project Grant (Pathobiology of Paget's Disease) to investigate the role of measles virus in the pathophysiology of Paget's disease and the role the genetic component plays in the pathologic process. His research on myeloma bone disease is also funded by The Department of Veterans Affairs Merit Review Grant and the Multiple Myeloma Research Foundation's Collaborative Program Grant.

Clifford Rosen

Dr. Clifford J. Rosen, M.D. is currently a Senior Scientist at Maine Medical Center's Research Institute. He is the Former Director of the Maine Center for Osteoporosis Research and Education an affiliate of St. Joseph Hospital, a Center which he started over 15 years ago. He currently oversees over 12 clinical research trials both Pharmaceutical and NIH funded studies. He is also Past President of the American Society of Bone and Mineral Research (ASBMR) 2002 – 2003. He also works as a Senior Staff Scientist at the Jackson Laboratory in Bar Harbor Maine studying IGF, IGFBPs on inbred strains of mice. He served 5 years as the first editor in Chief of the Journal of Clinical Densitometry the official Journal of the International Society of Clinical Densitometry. And currently serves as Associate Editor on the Journal of Bone and Mineral Research. His publications exceed 275 manuscripts published in a variety of Journals.

Graham Russell

Graham Russell (R G G Russell) is currently Professor of Musculoskeletal Pharmacology at Oxford University.

After graduating in Biochemistry from Cambridge University, he gained his PhD (on pyrophosphate metabolism) from the MRC Mineral Metabolism Unit at the University of Leeds. In 1965, he joined Dr Herbert Fleisch at the Medical Research Institute in Davos, Switzerland, initially to study the role of pyrophosphate in calcification. This work led directly to the discovery of the biological effects of bisphosphonates. The key studies were published in *Science* in 1969, in collaboration with Dave Francis, a physical chemist at Procter & Gamble. He then moved to Oxford University, where he completed his medical degree with distinction in 1971. Concurrently he continued research based at the Nuffield Department of Orthopaedic Surgery. Working with Roger Smith, this led to the first and successful clinical applications of bisphosphonates in Paget's disease of bone.

During the 1970s, he held appointments in the University of Berne with Herbert Fleisch (who sadly died in 2007),

and at Harvard University with John Potts and Stephen Krane as the Chiefs of the Endocrine and Arthritis Units respectively at the Massachusetts General Hospital, before moving in 1976 to the Department of Chemical Pathology in the University of Sheffield Medical School, under the leadership of Jack Martin. He became Professor and Head of Department of Human Metabolism and Clinical Biochemistry in 1977, and over the following years he helped to establish Sheffield as a major international centre for the study of basic and clinical aspects of bone diseases.

Graham Russell has worked on topics related to calcium metabolism and bone diseases throughout his career and is author of more than 500 publications. He has played a central role in studying the biological effects of bisphosphonates, and in their clinical development and evaluation for the treatment of bone disorders. Several bisphosphonates have become 'blockbuster' drugs and are still the drugs of choice for treating myeloma and cancer metastases in bone, as well as the leading drugs used in osteoporosis. During the past decade the molecular mechanisms of action of the bisphosphonates have been elucidated in detail. A key observation by Michael Rogers and others within his group in Sheffield revealed that nitrogen-containing bisphosphonates act as inhibitors of mevalonate metabolism, resulting in inhibition of protein prenylation. This in turn explains their ability to inhibit osteoclast activity. More recently working with Udo Oppermann and Jim Dunford, the Oxford group have solved the protein crystal structure of the target enzyme, farnesyl pyrophosphate synthase, and this is enabling further drug design, involving an on-going collaboration with Hal Ebetino.

He has held several national and international appointments in scientific and charitable activities related to bone disease and arthritis. He is currently Chairman of the Scientific Advisory Committee of the National Association for Pagets Disease (UK). From 1998-2001 he was the President of the International Bone and Mineral Society (IBMS). In 1986 he was one of the founding members of the National Osteoporosis Society (NOS, UK), which has grown to become one of the largest national charities devoted to osteoporosis.

Among awards, he has received the W F Neuman award of the American Society of Bone and Mineral Metabolism and the Pieter Gaillard Founders award of the IBMS. In 2008 he was elected a Fellow of the Royal Society of London.

In 2001 he moved back to the University of Oxford as the holder of the newly established Norman Collisson Chair of Musculoskeletal Sciences, and became a Professorial Fellow at St Peter's College. From 2003-6 he was Head of the Nuffield Department of Orthopaedic Surgery. He was the first Director of the Oxford University Institute of Musculoskeletal Sciences (the Botnar Research Centre), from 2002-7.

Natalie Sims

Dr Natalie Sims is a Senior Research Fellow of the National Health and Medical Research Council (Australia) and co-director of the Bone, Joint and Cancer Unit at St. Vincent's Institute in Melbourne. She completed her PhD studies on estrogen regulation of bone remodelling at the University of Adelaide in South Australia in 1994, then worked with John Eisman at the Garvan Institute in Sydney. Post-doctoral work at Yale University with Roland Baron delineated the importance of the estrogen receptors, growth hormone receptors and FosB in skeletal structure. She is recognised as an international authority on bone histomorphometric and *ex vivo* analysis of genetically-altered mouse models. Her main current research interest is the local control of osteoblast and osteoclast function including the roles of cytokines that work through gp130, with a goal of identifying pathways that may be manipulated to provide new therapeutic options for bone and joint disease.

Rajesh Thakker

Rajesh Thakker (MA, MD, FRCP, FRCP(Ed), FRCPath, FMedSci) is currently the May Professor of Medicine at the University of Oxford, UK. He commenced his pre-clinical medical training at Cambridge University with a BA in the Natural Sciences Tripos, and continued his clinical training at The Middlesex Hospital, London, UK. After qualifying, in 1980, he worked as a junior doctor at Northwick Park Hospital and The Hammersmith Hospital, and was medical registrar and an MRC Training Fellow at The Middlesex Hospital. He was appointed Consultant Physician and Endocrinologist at Northwick Park Hospital (MRC Clinical Research Centre), and as a Senior Lecturer at the Royal Postgraduate Medical School (RPMS) – The Hammersmith Hospital, in 1988. He remained at RPMS, where he became Professor of Medicine (1995), until 1999, when he took up his present position in Oxford. He has pursued a research programme, funded by the MRC (UK), which investigates the molecular basis of calcium disorders. He has been the recipient of many prizes which include Young Investigator Award from the ASBMR (USA), the Raymond-Horton Smith Prize (Cambridge University, UK), the Society for Endocrinology (UK) medal, the European Journal of Endocrinology Prize (EFES), and the Graham Bull Prize from the Royal College of Physicians (UK).

Wim Van Hul

Wim Van Hul, Ph.D., is professor in molecular genetics at the Department of Medical Genetics of the University of Antwerp, Belgium. The research activities of his team aim at the identification of genes involved in genetic bone disorders and obesity mainly by positional cloning. They made major contributions to the current understanding of the molecular genetics of sclerosing bone dysplasias with, for example, identification of genes involved in different forms of osteopetrosis and the identification of the SOST gene encoding sclerostin by studying patients with sclerosteosis and Van Buchem disease. Furthermore genetic association studies for both osteoporosis and Paget's disease have been performed. Finally, functional studies are being performed on the genes identified and the proteins they encode, to evaluate the effect of mutations detected within these genes.

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 chairman of five international conferences, serves as the president of the Croatian Calcified Tissue Society, is a member of the World Academy of Arts and Sciences (WAAS), European Molecular Biology Organization (EMBO) and founder of the biotech company Genera. He has authored more than 140 scientific 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 then 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:

Sunday 5 July:	16:00-19:00
Monday 6 July:	08:00-17:00
Tuesday 7 July:	08:00-17:00
Wednesday 8 July:	08:00-17:00
Thursday 9 July:	08:00-16:00

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

Meals
Dining times at St Catherine's College are as follows:

07:45-08:30 breakfast
12:45 lunch
19:00-20:30 dinner (Monday, Tuesday)
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

Sunday 5 July, 19:00
Dinner at Wadham College

Monday 6 July, 19:00
Dinner at St Catherine's College

Monday 6 July, 20.15
Post-dinner walking tour featuring some of Oxford's most historic pubs.
Please meet at the Porters' Lodge

Tuesday 7 July, 19:00
Dinner in St Catherine's College dining hall followed by music and conversation in the College Bar

Wednesday 8 July, 16:00
Bisphosphonates Anniversary Tea Party!

Wednesday 8 July, 19.30 for 20.00
Reception and Conference Dinner in St Catherine's College dining hall

Thursday 9 July, 19:00
Dinner at St Catherine's College

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

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