

IS1

EMBRYONIC STEM CELLS

Stephen Minger

Wolfson Centre for Age-Related Diseases, King's College London, UK

There has been significant interest in the therapeutic and scientific potential of human embryonic stem (ES) cells since they were first isolated in 1998. If human ES cells could be differentiated into suitable cell types, stem cells might be used in cell replacement therapies for degenerative diseases such as Type I diabetes and Parkinson's disease, or to repopulate the heart following myocardial damage. However, there is a significant shortage of high quality human ES cell lines and few research groups have experience in the propagation and manipulation of these cells. It is thus essential for the development of human stem cell technology, and the larger goal of cellular replacement therapy for human disease, that additional human cell lines are generated.

We are addressing this important issue using the combined expertise of the Stem Cell Biology Laboratory and the Assisted Conception Unit at King's College London. With local ethical approval and under licence from the UK Human Fertilisation and Embryology Authority, we have been establishing high quality human ES cell lines from a novel source of human embryos. To date, we have derived three human ES cell lines, including one that encodes the most common genetic mutation resulting in Cystic Fibrosis. In addition, much of our work is focused on the generation of human ES cell-derived, therapeutically important cell populations including neural, retinal, pancreatic, cardiac and endothelial stem cells. The tightly regulated yet permissive environment in the UK for human stem cell research, coupled with the government's commitment to the establishment of a centralised stem cell bank offers the UK the opportunity to be a leading player in the field of human regenerative medicine.

IS2

GENE THERAPIES IN MUSCULOSKELETAL DISEASE

Chris Evans

Harvard Medical School, Boston, MA, USA

Depending upon how you view the field, there are four main areas where gene therapy can be usefully applied to treat orthopaedic conditions (JAAOS 13: 230-242, 2005): Mendelian diseases, chronic complex diseases, cancer and tissue repair. Of these, a substantial body of literature exists only for chronic diseases, especially arthritis, and tissue repair. Arthritis is the most advanced of these applications, and there have already been four phase I clinical trials of gene therapy in subjects with rheumatoid arthritis. These have provided preliminary evidence of safety and efficacy. Animal models of osteoarthritis also respond to gene transfer and the first clinical trial in this area is under development.

Among the challenges for a successful gene therapy of a chronic condition such as arthritis is the need for prolonged periods of transgene expression. This is difficult and limits the choice of possible vectors for gene delivery. Tissue repair is an attractive additional target for gene therapy because a transgene will only need to be expressed for a short period of time-possibly just a few weeks. Moreover, the level of transgene expression may not need to be regulated very closely. Existing technology can already provide the necessary duration and level of transgene expression very effectively. Pre-clinical studies have demonstrated impressive healing of osseous lesions in response to the transfer of osteogenic genes. Gene-based approaches to cartilage repair are also a popular subject of research. Preliminary experiments have been conducted for improving the repair of meniscus, ligaments and tendon by gene transfer.

Collectively, the pre-clinical data are very encouraging and suggest an eventual clinical use of such technologies in certain settings. Among the issues that will determine the clinical utility of gene therapy in the orthopaedic context are safety, cost and feasibility.

IS3

GENETICS OF OSTEOARTHRITIS

John Loughlin

University of Oxford, Institute of Musculoskeletal Sciences, Botnar Research Centre, UK

Epidemiological studies, including twin-pair analyses and relative-risk studies, support a major genetic component to osteoarthritis (OA) susceptibility. OA is not however a Mendelian trait but instead falls in to the complex, multifactorial class of diseases. It has gradually become apparent that the nature of the OA genetic risk is likely to vary between different skeletal sites and may also vary between the sexes, although this latter observation is based on a small number of studies and needs further investigation to confirm its veracity.

With a genetic component established the next step was a hunt for the risk alleles. So far there have been four genome-wide linkage scans and two large-scale, gene-based SNP association studies performed on OA relative-pairs and case-control cohorts, respectively. The linkage scans revealed a number of highly significant loci, some of which have started to yield their susceptibility loci. The association studies have also identified a number of interesting hits. So far, robust data implicating the following genes has been generated: 1) the secreted frizzled-related protein 3 gene *FRZB* on chromosome 2q32.1 in a UK population; 2) the asporin gene *ASPN* on chromosome 9q22.31 in a Japanese population; 3) the calmodulin 1 gene *CALM1* on chromosome 14q32.11, also in a Japanese population and; 4) the leucine-rich repeat protein gene *LRCH1* on chromosome 13q14 in a UK and a Newfoundland population.

These recent findings suggest that OA genetic risk is acting principally on chondrocyte differentiation, proliferation and the general homeostatic balance of the cartilage extracellular matrix rather than through structural defects in the matrix. This is an important observation since signalling pathways are modifiable. The new genetics has therefore identified targets for new drug development as well as loci that can now be genotyped to identify at-risk individuals for more focussed clinical trials.

IS4

DNA METHYLATION AND THE SILENCING OF GENE EXPRESSION

John Newell-Price

Senior Lecturer in Endocrinology, University of Sheffield

DNA methylation is associated with silencing of gene expression. The predominant mechanism involves methylation of DNA and subsequent recruitment of binding proteins that preferentially recognize methylated DNA. In turn, these proteins associate with histone deacetylase and chromatin remodelling complexes to cause stabilization of condensed inactive chromatin. The opposite may also hold: targeting of methylation might depend on altered (repressed) chromatin structure.

To assess the impact of these mechanisms on gene expression we have been studying the Proopiomelanocortin gene (*POMC*) as a model system. *POMC* plays an essential role in the regulation of the hypothalamo-pituitary-adrenal axis, adrenal development and obesity. The peptide product, POMC, is cleaved to a variety of peptides including adrenocorticotrophin (ACTH), which in turn stimulates adrenal steroidogenesis, especially glucocorticoids, which in turn feedback to inhibit *POMC* expression. Excess glucocorticoid exposure, either endogenously produced or from therapeutic use, leads to osteoporosis, muscle atrophy, diabetes mellitus and hypertension – Cushing's Syndrome.

In ACTH-dependent Cushing's syndrome *POMC* is over-expressed. The highly tissue-specific 5' promoter of human *POMC* is activated in corticotroph adenomas of the pituitary and rarely may also be activated non-pituitary sites. The factors involved in transcription in the corticotrophs of the anterior pituitary gland are well delineated, but the mechanism of activation in non-pituitary sites is not fully understood. This promoter is embedded within a defined CpG island, and, in contrast to somatically expressed CpG island promoters reported to date, is methylated in normal non-expressing tissues, but is specifically unmethylated in expressing tissues, tumours and the *POMC*-expressing DMS-79 small-cell lung cancer cell line. Low-level DNA methylation in vitro is sufficient for silencing of expression. Active demethylation does not appear to occur, implying that methylation and expression patterns are likely to be set early in neoplastic transformation, and that targeted de novo

methylation might be a potential therapeutic strategy. To address whether a repressed gene is targeted for de novo methylation we have also assessed the effect of long-term suppression of *POMC* expression by glucocorticoids.

IS5

WEAR OF TOTAL JOINT REPLACEMENTS

John Fisher

University of Leeds, Leeds

Over two million total replacement joints are implanted in patients every year, and ten percent of the population of developed countries benefit from a joint replacement in their life times. Historically joint replacements were undertaken in the elderly, and with a conservative life style (1 million steps per year) and life expectancy of 10 to 20 years, tribological demands of between 10 to 20 million cycles were expected.

In the modern age, younger more active patients are demanding joint replacements. They have life expectancy of 20 to 40 years and an increased activity of up to 5 million steps per year means a ten fold increase in lifetime tribological demand of 100 to 200 million cycles. Wear and osteolysis is a common cause of failure in joint replacement, and increased tribological demands now requires high performance bearings in both hip and knee replacements. Additionally patients are demanding improved biomechanical function such as range of motion which in the hip requires larger diameter femoral heads in hip replacements.

Conventional metal or polyethylene bearing for hip replacements have been improved with the introduction of highly cross linked polyethylene which lead to a four fold reduction in wear. Unfortunately the debris released for highly cross linked polyethylene is smaller and more reactive and only results in a two fold reduction in functional osteolytic potential.

Alumina ceramic on ceramic bearings have substantially reduced wear and osteolytic potential compared to highly cross linked polyethylene, and are available in head sizes 28 to 36 mm.

Metal on metal bearings also have substantially lower wear than highly cross linked polyethylene and have the added advantage of being available in head sizes to 60 mm diameter. Additionally as a lubrication sensitive bearing the wear has been shown to decrease as the head size increases, again addressing both tribological performance and biomechanical function.

Research studies and the resulting development of prosthesis, have shown that a combination of biomechanical design and biomaterial combination can start to address the ten fold tribological demand of the young and active patient.

IS6

OSTEOCYTE MODIFICATION OF EXTRACELLULAR MATRIX

Lynda Bonewald

School of Dentistry, University of Missouri-Kansas City, USA

It is thought that the osteoblast initiates and controls all processes associated with and necessary for the production and mineralization of bone. It has been proposed that the osteoblast leaves behind within its trailing osteoid all proteins and organelles sufficient to initiate and propagate mineralization in a timely fashion and that the embedding osteoid-osteocyte becomes a static, inactive cell when it loses the majority of its cytoplasm, thereby simply existing for years or decades as a place holder in bone. Once surrounded by mineral, considerable data supports the function of a mature osteocyte as a mechanotranslating, signaling cell. However, data is starting to emerge that the osteoid-osteocyte may play a role in the mineralization process and that the mature osteocyte can modify its local environment.

As the osteoid-osteocyte embeds, it appears to generate mineralized, spherical structures of 50-200nm as the cytoplasm shrinks and dendritic processes extend. These structures dislodge from the cell surface and associate with collagen fibrils where they increase in size and coalesce to form mineralized bone. Proteins highly expressed in the embedding cell and the mature osteocyte such as E11, Dentin Matrix Protein 1, PHEX and MEPE are most likely playing a role in this process. Even once the cell is embedded in mineralized matrix, it has the capacity to influence its microenvironment.

For example, the number of canaliculi appear to increase with age. Another example is the response of osteocytes to agents such as steroids. Glucocorticoid not only induces osteocyte apoptosis, but the remaining viable (though compromised) osteocytes appear to have the capacity to enlarge their lacunae and leach mineral from the surrounding matrix. Capturing these changes has been difficult because osteocyte modification of their microenvironment takes weeks, months, or even years in contrast to the very rapid action of osteoclasts, hours and days, and the rapid action of osteoblasts, days and weeks. Therefore, the mature osteocyte may be a rapid responder with regards to mechanotransduction, but requires extended periods of time to modify its microenvironment.

IS7

SMALL LEUCINE-RICH PROTEOGLYCANS IN THE SKELETON

Marian F Young

Craniofacial and Skeletal Diseases Branch, NIDCR, NIH, Bethesda, MD 20892, USA

Small Leucine-Rich Proteoglycans (SLRPs) are major skeletal ECM components that comprise a family of 13 members containing repeats of a leucine-rich motif. To examine SLRP function, we generated mice deficient in one or more member and analyzed them at the tissue, cell and molecular levels. Mice deficient in biglycan (a class I SLRP) acquired early onset osteopenia due to a decreased ability to make new bone. Experiments using normal and biglycan deficient calvaria cells showed that biglycan controls BMP binding and activation. To attain a comprehensive picture of downstream effectors controlled by the presence of biglycan, microarray analyses was performed using mRNA from biglycan-deficient osteoblasts treated with or without BMP. Numerous differentially regulated mRNA's were identified related to cell cycle, differentiation and apoptosis. New molecular circuits potentially connecting biglycan to osteoblast function were uncovered and are currently under investigation. The observed defects in biglycan-deficient osteoblasts led us to speculate that biglycan could also modulate osteoclast function. Osteoblast-osteoclast co-culture and induced osteolysis experiments using normal and biglycan-deficient mice confirmed this theory. The SLRP decorin is closely related to biglycan and is up-regulated in the context of biglycan deficiency. To test whether there is redundancy/compensation in SLRP function, we made mice deficient in biglycan and decorin. These mice displayed a more profound osteopenia compared to mice deficient in only one of the SLRPs. To examine the molecular mechanisms that caused this osteopenia we cultured osteogenic bone marrow cells from the doubly deficient mice. We found these cells proliferate faster than normal cells but, unlike the singly deficient biglycan, they were not defective in differentiation. Moreover we found a "hypersensitivity" to TGF-beta that eventually led to premature apoptosis. This premature cell death appeared to deplete osteogenic precursors, and is the likely cellular basis for decreased osteogenesis in this animal model. To test compensation in distantly related SLRPs mice deficient in both biglycan (a class I SLRP) and fibromodulin (a class II SLRP) were made. They acquired early onset osteoarthritis caused by weak tendons that ossified prematurely. We plan to use these mouse models to identify early molecular events causing skeletal abnormalities dependent on SLRP function. This research was supported by the IRP-DIR, NIH.

IS8

WHAT IS INTERVERTEBRAL DISC DEGENERATION, AND HOW DOES IT AFFECT ADJACENT VERTEBRAE?

Michael A Adams

Department of Anatomy, University of Bristol, Southwell Street, Bristol BS2 8EJ, UK

The aims of this review are to a) distinguish intervertebral disc degeneration from growth, ageing, and adaptive remodelling, and b) to explain how disc degeneration alters the loading applied to vertebral bodies in such a manner that they becomes vulnerable to injury.

Proposed definitions: 1) the process of disc degeneration is an aberrant, cell-mediated response to progressive structural failure; 2) a degenerate disc is one with structural failure combined with accelerated or advanced signs of ageing; 3) early degenerative changes should refer to accelerated age-related changes in a structurally intact disc; 4) degenerative disc disease should be applied to a degenerate disc which is also painful.

Structural disruption plays a central role in these definitions because structural defects such as endplate fracture, radial fissures and herniation are easily-detected, unambiguous markers of impaired disc function. They are not inevitable with age, and are more closely related to pain than any other feature of ageing discs. Structural failure is irreversible, because adult discs have limited healing potential. It also progresses, by physical and biological mechanisms, and so is a suitable marker for a degenerative process. Biological progression occurs because structural failure uncouples the local mechanical environment of disc cells from the overall loading of the disc, so that disc cell responses become inappropriate or 'aberrant'. Animal models confirm that cell-mediated changes always follow structural failure due to trauma. This definition of disc degeneration simplifies the issue of causality: excessive mechanical loading disrupts a disc's structure and precipitates a cascade of cell-mediated responses leading to further disruption. Underlying causes of disc degeneration include genetic inheritance, age, inadequate metabolite transport, and loading history, all of which can weaken discs to such an extent that structural failure occurs during the activities of daily living.

Degenerated discs press unevenly on the vertebral bodies, concentrating stress anteriorly when the spine is flexed, and posteriorly when the spine is extended. Furthermore, in the usual upright postures, disc narrowing transfers up to 80% of compressive loading on to the neural arch. Consequently, anterior regions of the vertebral body become weakened and prone to wedge fractures.

IS9

DEVELOPMENTAL ORIGINS OF OSTEOPOROTIC FRACTURE

Cyrus Cooper

Professor of Rheumatology and Director, MRC Epidemiology Resource Centre, University of Southampton, UK

Osteoporosis is a skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. The cumulative incidence of fracture from age 50 years is estimated at around 50% among white women and 20% among white men. Preventive strategies against osteoporotic fracture can be targeted throughout the life course. Thus, modification of physical activity and dietary calcium/vitamin D nutrition in the elderly and during midlife, should complement high risk approaches entailing appropriate measurement of bone mineral density and targeting of anti-resorptive and formation stimulating drugs. Prevention of osteoporotic fracture can also be directed earlier in the life course. Environmental influences during early life interact with the genome in establishing the functional level of a variety of metabolic processes which are involved in the pathogenesis of osteoporotic fracture. The evidence that osteoporosis risk might be programmed in this way stems from four groups of studies: (1) Epidemiological studies which confirm that subjects who are born light and whose growth falters in the first year of postnatal life, have significantly lower bone size and mineral content, at age 60 to 75 years; (2) Epidemiological cohort studies have demonstrated that subsequent lower trajectories of childhood growth are associated with an increased risk of hip fracture among such men and women; (3) Detailed physiological studies of candidate endocrine systems which might be programmed have shown that birthweight and growth in infancy alter the functional settings of the GH/IGF-1, and hypothalamic pituitary adrenal axes; (4) Studies characterising the nutrition, body build and lifestyle of pregnant women which relate these to the bone mass of their newborn offspring, have identified a number of important determinants of reduced fetal mineral accrual (maternal smoking, low maternal fat stores and maternal vitamin D deficiency, intense levels of weight-bearing physical activity in late pregnancy). Follow-up studies of randomised controlled trials of vitamin D supplementation in infancy suggest persisting benefits in adolescence and young adulthood. These data suggest that undernutrition and other adverse influences arising in fetal life or immediately after birth have a permanent effect on body structure, physiology and metabolism, which might independently influence the later risk of cardiovascular disease and osteoporotic fracture.

IS10

DETERMINANTS OF BONE GROWTH IN CHILDHOOD: INSIGHTS FROM THE ALSPAC COHORT

Jonathan Tobias

University of Bristol

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a unique population-based birth cohort, recruited from approximately 14,000 pregnant women between 1991-2. We have used this study to investigate determinants of bone development in childhood, based on total body DXA scans performed in 7333 and 7006 children at age 9.9 and 11.8 years respectively, using a Lunar Prodigy. This presentation will focus on recent findings which suggest a hitherto unrecognised influence of adiposity on periosteal bone growth, based on our results for height-adjusted total body bone area. Initially, we examined how social position affects bone development, by linking measures of social position such as level of maternal education, ascertained by questionnaire completed during pregnancy, to age 9.9 DXA data. Higher social position was found to be inversely associated with height-adjusted total body bone area. On the other hand, higher social position was positively associated with bone area after adjusting for weight. These findings suggest that social position exerts opposing effects on bone growth, such that higher social position increases bone size through effects on longitudinal growth, whereas lower social position enhances periosteal growth through effects on weight.

This suggestion that weight is an important determinant of periosteal growth led to further studies which highlight the role of adiposity in bone development. For example, we found that fat mass mediates the effect of weight on the relationship described above between social position and bone area. In addition, our subsequent studies revealed that fat mass as measured by DXA at age 9.9 years is an important positive determinant both of bone area at age 9.9, and of percentage increase in bone area over the following two years, even after adjustment for height and lean mass. We then examined whether effects of physical activity on fat mass modify those on the skeleton. An inverse relationship was observed between height-adjusted bone area, and moderate and vigorous physical activity (MVPA) as assessed by accelerometer recordings, in 4457 age 11 children. However, MVPA was positively related to bone area after adjusting for both height and fat mass. These findings suggest that although MVPA stimulates periosteal bone growth, this action is opposed by the tendency of MVPA to reduce fat mass. Taken together, our findings suggest that adipose tissue represents an important influence on bone development in childhood, though the mechanisms involved remain to be elucidated.

IS11

SKELETAL TISSUES AT THE NANOSCALE

Abstract not received

IS12

BONE FRAGILITY IN CHILDHOOD

Nick Bishop

University of Sheffield and Sheffield Children's Hospital

If bone fragility is reflected in a high risk of fracture, then it would appear that as a group children have bones that are as fragile as those of the elderly. Fractures are common in childhood; around one third of children will fracture at least once by age 17 years and the peak age-specific incidence of fractures in boys of 3% and 1.5% in girls is surpassed only by that of women over 85 years and not at all in men.

Fractures are commoner at all ages from 2-17 in boys. For boys and girls, fracture incidence peaks around the time of maximal height velocity. Children who fracture appear to have reduced bone mass for body size compared with those who do not fracture. Cohort studies suggest an increased risk of fracture in children receiving inhaled therapy for asthma, but this has not been confirmed in case control studies. Recurrent fractures occur in approximately 6% of children. Recurrent fractures are

more common in children who are overweight and physically less active, in those who avoid milk and in those who consume excessive quantities of carbonated drinks.

There are a number of disorders that predispose to fractures with low bone mass in infancy and childhood; these include osteogenesis imperfecta, idiopathic juvenile osteoporosis and metabolic bone disease of prematurity. Great progress has been made in the treatment of these disorders over the last 10 years, particularly with the introduction of bisphosphonate therapy as part of multidisciplinary management for the osteoporotic disorders. The diagnosis of bone fragility in infancy and its differentiation from child abuse remains a contentious issue.

IS13

THE LINKS BETWEEN BODY COMPOSITION AND BONE

Ian R Reid

University of Auckland, New Zealand

Body weight impacts on both bone turnover and bone density, and is therefore an important risk factor for vertebral and hip fractures, ranking in importance alongside that of age. The effect of body weight is probably contributed to by both fat mass and lean mass, though in postmenopausal women, fat mass has been more consistently demonstrated to be important. A number of mechanisms for the fat-bone relationship exist and include the effect of soft tissue mass on skeletal loading, the association of fat mass with the secretion of bone active hormones from the pancreatic beta cell (including insulin, amylin, and preptin), and the secretion of bone active hormones (eg, estrogens and leptin) from the adipocyte. These factors alone probably do not fully explain the observed clinical associations, and further study of the actions on bone of novel hormones related to nutrition is an important area of further research. An understanding of this aspect of bone biology may open the way for new treatments of osteoporosis. More immediately, the role of weight maintenance in the prevention of osteoporosis is an important public health message that needs to be more widely appreciated.

IS14

FUTURE MANAGEMENT OF FRACTURE RISK

Abstract not received

IS15

NICE GUIDELINES

Richard Keen

The Royal National Orthopaedic Hospital, Stanmore. UK

In the UK, the National Institute for Health and Clinical Excellence (NICE) is an independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health. NICE publishes guidance which aims to ensure that promotion of good health and patient care in the NHS are in line with the best available evidence of clinical effectiveness and cost effectiveness. NICE guidance falls into 3 categories: Interventional Procedures, Technology Appraisals and Clinical Guidelines.

With relevance to osteoporosis, guidance on the interventional procedures vertebroplasty and kyphoplasty was initially published in September 2003, with revised recommendations published in April 2006.^{1,2} Both these techniques are now approved for use in patients with painful vertebral fractures refractory to more conservative treatment. These procedures should only be undertaken with prior discussion by a specialist multidisciplinary team that includes a radiologist and a spinal surgeon, and when there are facilities for good imaging, and arrangements for good access to a spinal surgery service. Clinicians should also have received training to reach an appropriate level of expertise before carrying out these procedures.

The technology appraisal on treatments for established postmenopausal osteoporosis was published in January 2005.³ This guidance reviewed the evidence for bisphosphonates (alendronate, etidronate and risedronate), raloxifene and teriparatide. Interventional thresholds for treatment were defined on the basis of age, BMD and clinical risk factors. This guidance is now being updated to include strontium

relate, although it will not review the evidence for other drugs that are now available such as ibandronate. The Appraisal Consultation Document (ACD) on this area will be published in late July 2006. In addition, a further ACD will be published at this time on the treatment of primary osteoporosis. This presentation will critically review some of the key data and assumptions that are being included in the NICE models, and the potential impact this guidance will have on clinical practice.

The development of clinical guidelines will assist in the management of osteoporosis other than postmenopausal disease (i.e. secondary disease, osteoporosis in men, paediatric osteoporosis). It is hoped that these guidelines will also include information similar to the WHO risk algorithm to assist in calculating an individual patient's 10-year risk of fractures. Recommendations for follow-up and monitoring will also be useful for clinical practice. To date, no draft of these guidelines has been published.

References

1. National Institute for Clinical Excellence. Percutaneous vertebroplasty. Interventional Procedure Guidance Sept 2003. (<http://www.nice.org.uk/pdf?ip/IPG012guidance.pdf>)
2. National Institute for Clinical Excellence. Balloon kyphoplasty for vertebral compression fractures. Interventional Procedure Guidance April 2006. (<http://www.nice.org.uk/page.aspx?o=IPG166guidance>)
3. National Institute for Clinical Excellence. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Health Technology Appraisal 87; Jan 2005. (<http://www.nice.org.uk/TA087guidance>)

IS16

RISK ASSESSMENT

John A Kanis

WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK

At present, treatment is largely directed on the basis of bone mineral density (BMD). In the UK, treatment is recommended when the T-score for BMD is found to be less than -2.5 SD. The same T-score has, however, quite a different significance at different ages. For example, the 10-year probability of hip fracture for women in the UK with a T-score of -3 SD is 3.2% at the age of 50 years, but 19.8% at the age of 80 years. Thus, fracture risk prediction is optimised by integrating information on risk factors that contribute to fracture risk independently of BMD. A major programme of the WHO Collaborating Centre at Sheffield has been to identify and validate readily used risk factors.

Risk factors for fractures have been identified from 12 prospective population-based cohorts comprising 250,000 person-years of observation with 3,500 osteoporotic fractures. Clinical risk factors that contribute to fracture risk independently of BMD include age, previous fragility fractures, a family history of fracture, rheumatoid arthritis, smoking, exercise, alcohol and the use of oral glucocorticoids. Their combined use with (or without) BMD enhances the sensitivity of fracture prediction without sacrificing specificity. The utility of the risk factors has been validated in the independent population-based cohorts of 230,000 individuals followed for 1.2 million person-years.

The ability to assess fracture risk from clinical risk factors permits intervention in men and women that is based not solely on BMD. Therefore, diagnostic thresholds for osteoporosis (based on BMD) differ from intervention thresholds. Because of the many techniques available for fracture risk assessment, the ten year probability of fracture is the desirable parameter to determine intervention thresholds. The setting of intervention thresholds is ultimately dependent on health economic considerations. When BMD is used as a test alone, an intervention threshold of -2.5 SD is cost-effective. In the presence of other independent risk factors less stringent criteria are appropriate so that intervention can be directed to individuals where hip fracture probability ranges from 2% to 10% (depending on age). These thresholds, derived from Sweden or the UK, require modification in

different countries to take account of different costs and risks that vary markedly in different regions of the world.

IS17

OSTEOPOROSIS TREATMENT IN THE BIOLOGICS ERA

Richard Eastell

Academic Unit of Bone Metabolism, University of Sheffield

We have several treatments licensed for osteoporosis, or in the clinical development phase. Some of these have been developed as a result of our better understanding of bone biology. The two that I will discuss are the antibody to RANK-L (denosumab) and the 1 to 34 fragment of parathyroid hormone (teriparatide). The RANK-L pathway is critical in the control of bone resorption, and a number of approaches have been developed to inhibit it, including the use of OPG, RANK-fc, and RANK-L antibodies. The last of these is now in Phase III clinical trials and has been shown in postmenopausal women to have effects on bone turnover markers and bone mineral density that are at least as great as the bisphosphonate alendronate. The onset and offset of these effects are rapid. The potency of this agent on bone resorption may make it effective in other disorders of high bone remodelling. Teriparatide is the 1 to 34 N-terminal fragment of parathyroid hormone and is licensed for the treatment of severe osteoporosis. It is given by daily subcutaneous injection. It results in a large and early increase in bone formation markers and bone histomorphometry had shown that this reflects the production of de novo bone formation on quiescent trabecular surfaces as well as periosteal new bone formation. The resulting large increases in bone mineral density have been associated with a reduction in the rates of vertebral and non-vertebral fractures. There are questions that remain, 1) can it be given by other routes; 2) which patients benefit most; 3) how should it be used with anti-catabolic therapy (before, during or after) and should multiple courses be given?

IS18

VITAMIN D – WHO NEEDS SUPPLEMENTATION AND WITH WHAT?

Frazer Anderson

University of Southampton

Vitamin D (calciferol) is not really a vitamin at all, as it is synthesised endogenously in sunlight-exposed skin. Calciferol is a steroid hormone precursor which in its activated form, calcitriol, regulates calcium uptake from the gut and renal calcium handling. Deficiency depletes the skeletal calcium reservoir, causing osteomalacia, rickets and osteoporosis. Deficiency also impairs neuromuscular co-ordination, influencing falls risk. Additionally, calcitriol mediates some aspects of cell growth and differentiation, with putative roles in autoimmunity, allergy and carcinogenesis.

Recommended dietary intake levels of vitamin D are difficult to establish. It is highly unusual for any endocrine pathway to depend on external supply of the pre-hormone, which suggests that skin synthesis is the more physiological source.

Calciferol is sequestered in fat and calcitriol synthesis is tightly controlled by regulation of hydroxylation in the kidney. Vitamin D status is therefore assessed by measurement of its circulating intermediate metabolite, 25-hydroxy-calciferol (25-OH-D). Levels below about 20nmol/l are clearly associated with osteomalacia and are described as “deficiency”, but calcium homeostasis remains abnormal at 25-OH-D levels up to around 50-70nmol/l. This suboptimal range is referred to as “insufficiency” and there is considerable controversy over where to set its upper limit, with US authorities favouring higher limits than most others. These higher target levels are effectively unachievable through diet alone.

Vitamin D insufficiency is very common in older people, and supplementation is widely advocated for the prevention of bone disease. It is available as either vitamin D3 (colecalciferol), identical to the molecule made in human skin, or vitamin D2 (ergocalciferol), produced by irradiation of fungi. D2, which is cheaper to manufacture, is effective for the prevention of osteomalacia/rickets, but there is growing evidence that it is much less potent than D3 in maintaining optimum calcium balance.

Clinical trials of vitamin D supplements for fracture prevention have shown conflicting results and there is no consensus on their interpretation. Current thinking in the UK favours offering combined

vitamin D3 (700-800iu) and calcium supplements to housebound older people and care home residents for primary fracture prevention, and as an adjunct to anti-osteoporosis drugs such as bisphosphonates for secondary prevention.

IS19

THERAPEUTIC CELL THERAPY AND TISSUE ENGINEERING: NOVEL MAGNETIC STRATEGIES FOR GROWTH CONTROL AND DELIVERY

Alicia El Haj

Institute of Science and Technology in Medicine, Keele University Medical School, University Hospital of N. Staffs, Stoke on Trent

New therapies involving cells have enormous potential for applications in regenerative medicine and treatment of disease - the challenge lies in controlling the behaviour and activity of these cells in vitro and in vivo. Enabling technologies are being developed which allow us to grow and condition cells in vitro. These technologies facilitate the growth of tissues in a 3D environment and enable physiologically relevant cues such as mechanical strain to be delivered in vitro and ultimately in vivo. In addition, new technologies are being developed which allow delivery of cells in a patient and maintenance of these cells at the site of repair. In our lab, we are investigating the use of magnetic strategies to manipulate and control differentiation of cells in a bioreactor environment or remotely in vivo in the patient. In this presentation, we report our recent work on tagging specific mechanosensitive receptors with magnetic nanoparticles which results in downstream cell signalling and gene activation using time varying remote magnetic fields. This technique is applicable to monolayer cultures and cell seeded 3D constructs for tissue engineering of bone and cartilage. By controlling the mechanosensors directly on the cells within the construct, we are no longer reliant on using slow degrading materials which are capable of withstanding significant load bearing for bone tissue engineering thus enhancing rapid turnover and construction of biological matrices in vitro. Using a magnetic force bioreactor developed in our lab, we describe our new strategies for internalisation of magnetic nanoparticles which can bind to key receptor sites on the internal membrane. A comparison of receptor sites tagged such as integrins and ion channels will be described with resultant effects on bone cell signalling and formation. Recent work has investigated conditioning of MSCs (Poetics, Ltd) in monolayer culture demonstrating an upregulation of bone cell markers such as osterix, CBFA1 and osteopontin after 1 week of cyclical loading in culture. The magnetic nanoparticle technology has the potential to be applied directly in vivo in animals models and ultimately in clinical treatments. We describe recent investigation into localisation of stem cells in vivo using magnetic tagging.