

Connective Issues



BSMB Newsletter

Committee:

Prof. Ray Boot-Handford (Chairman), Prof. Andrew Pitsillides (Secretary),
Dr. David Young (Treasurer), Dr Jo Adams, Dr Emma Blain, Dr. Sarah Howat,
Dr Philippa Hulley, Ms. Eleanor Jones, Dr Chris Murphy, Dr. Mandy Plumb and
Dr Tonia Vincent

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Contents

- 2 Editorial.....*Andy Pitsillides*
- 2 Chairman's letter.....*Ray Boot-Handford*
- 3 BSMB News
 - 2011 BSMB Fell-Muir Award to.....*Professor Bruce Caterson*
- 3 Mark your Diary!
- 4 BSMB meeting, September 2011.....*Details for Newcastle*
- 5 BSMB meeting, April 2012..... *Details for Oxford*
- 6 Conference Bursaries from BSMB.....*Mandy Plumb*
- 7 Young Investigator Award and Prizes
- 7 Meeting Report*Bristol, Spring 2011*
- 17 Current BSMB committee.....*Contact Information*
- 17 Welcome to New Members
- 18 Obituary.....*John Chapman*
- 20 Flyer: BSMB Newcastle meeting..... *Register now - print and post*

Editorial

Dear BSMB Members

Welcome to the 78th Connective Issues and my first as Honorary Secretary. Some things change, some things don't change. After fantastic service, the Committee reluctantly consented to John Couchman stepping down as Honorary Secretary. I can vouch to John's great support and invaluable encouragement throughout my time as a Committee member. Without wishing to step on Ray's toes (see Chairman's letter), I'd like to thank John for his truly outstanding contribution - I'd also like to thank him for the memory stick containing the historical evidence of his contribution over the last seven years.

Some things don't change. Register, if you haven't already, for the Autumn meeting in Newcastle. An exciting, broad and innovative programme created by David Young and Drew Rowan has produced a meeting not to be missed. I hope you can attend and that you will continue the tradition of BSMB meetings based on good science and a lively and enjoyable environment. Howay the lads!

I need also to share with you the news that vacancies for the BSMB Committee will be announced in the January newsletter, as those whose term will be complete, will need to be replaced at our 2012 meeting in Oxford.

You may spot some changes. I have added a 'Mark your Diary!' and a 'BSMB News' section, to which I hope you will contribute. If you have any news, comments, events, or a letter that you'd like shared with members in the next Newsletter (be mindful that only two issues are published each year) please send me the details (apitsill@rvc.ac.uk). Other plans include the introduction of shorter meeting reports, do you like the idea?

Finally, having been elected, I thought I'd look up 'honorary' to help inform my role into the future. It means either: *'conferred as an honor', without requirements or functions (as in 'honorary' doctorate) or 'unpaid' (as in Honorary Secretary)*. I look forward to serving and with your help will hopefully leave the Society as robust as it was found.

Andy Pitsillides,
Honorary Secretary

Chairman's Letter

Dear Fellow Matrix Biologists,

As usual, we held the Society AGM at our spring meeting in Bristol, organised very ably by Wa'el Kafienah and Anthony Hollander. One function of the AGM is to renew and refresh the organising committee and each year we lose 2-3 established committee members and gain new members to replace them. This year, John Couchman retired as our Honorary Secretary.

John's association with the committee started in an unusual fashion. Normally, people join the committee and toward the end of their term they organise one of our meetings. In John's case, he first organised a highly successful BSMB meeting at Imperial College to mark Roger Mason's retirement in autumn 2003 and then became member of the organising committee at the AGM the following spring (2004). In spring 2006 John was elected to the role of Honorary Secretary. John has been an exemplary Secretary of the Society. Throughout John's tenure, he organised most aspects of the day to day running of the Society and ensured the Society was always on a forward trajectory. John brought great vision to the post and has carefully guided the Society over the past 4 years. I would like to personally thank John for making my life as Chairman so simple over the past 2 years and thank him on behalf of the Society for all the hard work he has put in over the past 7 years.

Jelena Gavrilovich left the committee last autumn after serving an extended 'stint' to enable her to organise the September 2010 meeting at UEA on 'Inflammation and matrix biology'. Wa'el Kafienah retired from the committee this Spring following his meeting on 'musculoskeletal repair and regeneration'. I thank both both Jelena and Wa'el for all their efforts on behalf of the Society. We welcome the return of Andy Pitsillides to the committee as our new Honorary Secretary and this will certainly liven up committee meetings in the future! We also welcome Jo Adams as a committee member.

Over recent years we have experienced increasing difficulties in finding University accommodation for our spring meetings as

many (Manchester, Bristol, Cardiff to name but three) have stopped vacating student accommodation over the Easter period for conference hire. If your institution can provide conference accommodation over the Easter period, please let me know.

Fortunately, one such venue is St Catherine's College Oxford where we will be holding our Spring 2012 meeting. This will be special for several reasons. Firstly, it is a Joint Meeting with our colleagues from the German Matrix Biology Society (organised by Mandy Plumb, Philippa Hulley, John Couchman and Liliana Schaefer) and it will cover multiple themes (see preliminary programme included later in newsletter). Secondly, the German Society will be celebrating its 25th Anniversary at Oxford. Thirdly, the meeting will be larger than normal due to a significant attendance of the German Society members and it will last for a day longer than usual. Fourthly, this will be our only meeting in 2012 due to the fact that our normal Autumn meeting would clash with FECTS 2012 which is being organised for the end of August (rather than July when the European football championships are taking place in Poland). BSMB will be offering a significant number of bursaries to help younger members attend these meetings in 2012. Finally, I hope to be able to welcome you all to our Newcastle meeting in September (8th-9th) on the topic of matrix signalling in health and disease which will include our BSMB Young Investigator Award.

Ray Boot-Handford
Chairman

BSMB News

Subscription reminder

We'd like to take this opportunity to remind our members who pay their subscriptions by means other than standing order, that the membership fees for 2011-12 are now probably overdue. An up to date membership list and a clearer idea of our Society's funds are clearly helpful in our budgeting for the future - so please pay your subscriptions if they are due.

Professor Bruce Caterson receives 2011 Fell-Muir Award



Professor Bruce Caterson, University of Cardiff receives the Fell Muir Award from BSMB Chairman Prof. Ray Boot-Handford (left) and Secretary Prof. John Couchman after his lecture at the Bristol meeting 2011. The Fell-Muir is awarded to a senior investigator in recognition of an outstanding contribution to matrix biology and the BSMB.

Abstracts and Meeting report from the 2011 Bristol meeting will be published later this year in International Journal of Experimental Pathology (also sponsors of the Fell-Muir), who are gratefully acknowledged for their continuing support. The meeting report can be also accessed on the BSMB website (<http://www.bsmb.ac.uk>).

Mark your diary!

* *BSMB Autumn Meeting - Newcastle, 2011*
Thursday 8th - Friday 9th September

Matrix signals!

Cell-matrix interactions in health & disease
Registration now open www.bsmb.ac.uk

* *BSMB Meeting - Oxford, 2012*
2nd-4th April (German Matrix Biology Society)

Matrix Molecular Biology:

Integrator of Tissue Function and Disease
(see below for details)

BSMB 2011 Autumn Meeting

'Matrix signals! Cell-matrix interactions in Health and disease'

Organised by Dr. David Young & Prof. Drew Rowan, University of Newcastle.

September 8-9th 2011. University of Newcastle

The meeting will explore how cells sense and respond to their surrounding matrix. Cells remodel matrix, resulting in matrix fragments and neo-epitopes which provide a feedback loop. The meeting will cover aspects of normal and aberrant matrix degradation, receptor-mediated matrix sensing and signalling in both health and disease.

Interactive poster sessions and a number of short oral communications selected from the abstracts mean the meeting will cover many aspects of current matrix biology research. An additional highlight of the meeting will be the BSMB Young Investigator lecture. This will be given by the winner of a competition open to young BSMB members, in which the prestigious award comes with a £1000 prize.

The conference dinner will be held at St. James' Park, home of Newcastle United Football club.

Oral presentations in all sessions will be selected from submitted abstracts. This includes the Open BSMB session where all topics related to matrix biology will be covered. Poster sessions will be an important component of the meeting and will embrace all aspects of matrix biology.

Session 1: Matrix mechanical forces

Akiko Mammoto (Boston). How extracellular matrix (ECM) and mechanical forces regulate cellular signal transduction.

Tony Poole (New Zealand). Primary cilia and mechanobiology.

Session 2: Matrix receptors

Attila Aszodi (Germany). Chondrocyte polarity and cartilage function: the role of cell-matrix interactions.

Christoph Ballestrem (Manchester). Adhesion Signalling

Session 3: Matrix Receptors/Sensing

Birgit Leitinger (London). Discoidin domain receptors: adhesion and transmembrane signalling.

Session 4: Matrix signalling fragments

Suneel Apte (Cleveland). Versican proteolysis by ADAMTS proteases and its impact on mouse development.

Kim Midwood (London). Unique signalling pathways induced by tenascin-C fragments

Session 5: Matrix signalling in disease

Wim van den Berg (Netherlands). Alarmins in arthritis.

Benjamin Alman (Toronto). HH/Wnt in OA

Key dates:

- **Registration** is now open and closes on **August 11th 2011** after which a late fee of £30 will apply, so please register without delay!
- **Abstract Deadline August 11th 2011**
- **Bursary application Deadline August 11th 2011 (applicants will be notified by August 18th)**

**BSMB 2012 Meeting - Oxford
2nd-4th April 2012**

**Jointly with the German Matrix
Biology Society**

***'Matrix Molecular Biology:
Integrator of Tissue Function and
Disease'***

Organised by

**Mandy Plumb, Philippa Hulley, John
Couchman and Liliana Schaefer**

We are extremely happy to join forces with the German Matrix Biology Society in organising this meeting. A clash with FECTS 2012 later in September and the opportunity in sharing with our colleagues in their 25th Anniversary celebrations means that BSMB will not be running an Autumn meeting during 2012. All members are therefore urged to attend what looks like being an exciting meeting in Oxford. It will be a three-day meeting in order to accommodate the very welcome inclusion of our matrix biology partners from the German Society. The programme is very varied and has a broad range of international and national (both UK and German) invited speakers.

The preliminary programme includes:

Session 1: Mechanobiology of the Matrix, with **Valerie Weaver** (Univ. California, San Francisco) and **Paddy Prendergast** (Dublin) as invited speakers.

Session 2: with **Clare Waterman** (NIH) and **Joachim Spatz** (MPI Stuttgart) speaking about Nanotechnology and cell adhesion. Award of the 2012 FELL MUIR AWARD

Session 3: Stem Cells and their niche, with **Francesco dell'Accio** (QMUL, London) and **Cathy Merry** (Manchester) as speakers.

Session 4: Matrix and Cancer. Invited speakers to include **Kebs Hodivala-Dilke** (QMUL, London) and **Yoshifumi Itoh** (Imperial College London)

Session 5: Tissue injury and repair with **Eric Olson** (University of Texas, South Western Medical Centre) and **Dietmar Vestweber** (Munster)

Session 6: Wound healing/Inflammation including talks from **Liliana Schaefer** and **Paul Martin** (Bristol)

Session 7: Fibrosis with **Oliver Eickelberg** (Munich) and **George Bou-Gharios** (Imperial College London) as invited speakers.

Session 8: with **Reinhard Fassler** (Munich) and **John Couchman** (Copenhagen) as invited speakers on Cell Adhesion and Signalling

**Tendon Symposium
'Tendon Biology and Pathology'
(under the auspices of BSMB)**

September 3rd - 4th, 2012

**Organiser: Dr. Graham Riley,
University of East Anglia
Graham.Riley@uea.ac.uk**

This meeting will focus on the latest research findings in tendon biology and pathology. The programme for the meeting is being finalised, but there will be contributions invited from most of the groups active in tendon research in the UK. Keynote speakers include Chris Evans (Harvard), Kathe Derwin (Cleveland Clinic) and Michael Kjaer (Copenhagen)

More details will be available on the BSMB website.

Conference Bursaries from the BSMB

Mandy Plumb

Young members of BSMB are encouraged to apply for bursaries to assist in expenses associated with attending the Spring or Autumn BSMB meetings or other selected meetings, such as those organised by the Federation of the European Connective Tissues Societies (FECTS). Applicants should be at an early stage of their career and, therefore, emphasis is given to young researchers such as graduate students and early post-docs. The BSMB bursary scheme has two distinct application routes:

Conference Presenter Bursaries

BSMB offer 4 bursaries for 'Conference Presentation' for young researchers wishing to present their research at BSMB meetings. The research must be relevant to BSMB but need not be on the theme of the meeting. Applications must be accompanied by an abstract of the research to be presented. Where numbers of applications exceed the number of available bursaries, the quality and impact of the science and record previous bursary support will be taken into account.

Conference Reporter Bursaries

The BSMB will offer 3 'Conference Reporter' bursaries for BSMB meetings. Applicants undertake to write a report on the talks at the conference for publication on the BSMB website and subsequently in the International Journal of Experimental Pathology. This is an excellent opportunity for individuals to develop their scientific writing and reporting skills. If desired, reports can be attributed to the individual reporter responsible, enabling the resulting publication to be used by the authors as examples of output in any Portfolio of Professional Skills Development. Applicants need not be presenting a poster at the meeting. If applications exceed the number of bursaries available, the scientific impact of the work and previous BSMB support will be taken into consideration.

The bursaries (<£200) will cover conference expenses (e.g. registration, accommodation, conference dinner) and contribute towards travel costs. In exceptional circumstances, a

request for further assistance with travel costs may be considered by the committee ([travel bursaries](#)).

Qualification criteria

To qualify for a bursary, applicants need to have been a BSMB member for at least 3 months prior to the opening of registration for the meeting. *Applicants must therefore have joined BSMB before 9th May 2011 to be eligible for Newcastle meeting bursary.*

Application procedure

Applications must be sent by e-mail to Ms. Jane Lohmann (J.M.Lohmann@bristol.ac.uk).

Closing date for the BSMB Autumn Meeting: 11th August 2011. Successful applicants will be notified on or soon after 18th August 2011.

Full details and application forms available at <http://www.bsmb.ac.uk/> under 'Bursaries'.

Recent bursary awards

BSMB awarded 8 bursaries for the Spring 2011 Meeting in Bristol.

Reporter Bursaries: Miss Natasha Agabalyan (Brighton and Sussex Medical School), Mr Matthew Mayhew (University of East Anglia) and Mr Henry Jia (University of Bristol) who produced the comprehensive report of the meeting presented in this Newsletter.

Presenter Bursaries: Dr Cleo Bonnet (Cardiff University), Miss Sarah Turner (ARC, Robert Jones & Agnes Hunt Orthopaedic Hospital), Dr Raewyn Poulson (University of Oxford), Mrs Niina Hopper (University of Cambridge) and Dr Maan Al-Abbasi (university of Bristol).

A further 8 bursaries were awarded in 2011 to support attendance of several International matrix biology-related conferences.

Eleanor Jones: ORS 2011

Kirsten Legerlotz: ORS 2011

Andrew Hamilton: Int. Angiogenesis meeting

Kate Williamson: Int. Angiogenesis meeting

Louise Kung: Gordon Conference Collagen

Chloe Young: Gordon Conference Collagen

Douglas Dyer: Immunology Conference

Steven Woods: Keystone Symposium miRNA

Young Investigator Award and Poster Prizes from the BSMB

At Newcastle the BSMB Young investigator Award for 2011 will be presented.

- [Young investigator Award](#)

Poster Prizes are given at every meeting:

- [Poster prize information](#)
-

British Society for Matrix Biology - Spring 2011 Meeting Report

written by **Natasha Agabalyan,
Matthew Mayhew and Henry Jia**

Advances in Musculoskeletal Repair and Regeneration

Organised by **Wael Kafienah,
School of Cellular & Molecular Medicine,
University of Bristol**

The Spring 2011 BSMB meeting was hosted by Bristol University on 11th and 12th of April and organised by Dr Wael Kafienah, with support from Jane Lohmann, Jan Cunningham and Prof Anthony Hollander. The meeting was held in the Wills Memorial Building. It was attended by ~130 delegates and comprised 5 sessions, each focused on a particular tissue in the musculoskeletal unit: bone, cartilage, tendons and ligaments and skeletal and cardiac muscle, with an additional Open Session. In addition to scientific presentations, Dr Michael Patnick, Head of Research and Education at Arthritis Research UK highlighted fellowship and funding opportunities. The prestigious IJEP-sponsored Fell-Muir Award was presented to Prof Bruce Caterson, Cardiff University for his work on Glycosaminoglycan Glycobiology.

Mr Steven Woods (Newcastle University), Dr Siyuan Li (Cardiff University) and Miss Sian

Morgan (Cardiff University) were awarded Poster Prizes (sponsored by the International Journal of Experimental Pathology). It is vital to stress that the many bursaries provided to support attendance of this meeting were possible due the subscriptions paid by your BSMB membership and demonstrates our pledge to sustain and secure future matrix biology research into the future.

The meeting was generously sponsored by Thermo Scientific (Platinum), Company of Biologists, Development, The Journal of Experimental Biology, Disease Models and Mechanisms, Journal of Cell Science (Gold), National Stem Cell Network UK (Silver), Life technologies, Merck Millipore, MACS Miltenyi Biotec, PeproTech, Promega, R&D Systems, Roche, Sigma-Aldrich, Scientific Laboratory Supplies and VWR (Bronze).

Session 1 - Bone

Chaired by Prof Andy Pitsillides (Royal Veterinary College) and Dr Simon Tew (University of Liverpool), this opening session began with an exciting presentation by **Prof. Gordana Vunjack-Novakovic** (Columbia University, New York) entitled '*Craniofacial Tissue Engineering*'. She stressed the importance of tissue engineering, stating that as we live longer, we need spare parts and that bioengineering will help unlock the full regenerative potential of stem cells, to provide the dream of 'staying forever young'. Prof. Vunjack-Novakovic stated a surprising figure that two thirds of people who have ever reached the age of 65 in the history of civilisation are alive today, with life expectancy in classical Greece a mere 28 years; relatively recent advances in medicine bumping up this figure only since the 20th Century. Prof. Vunjack-Novakovic went on to describe that cells respond to the entire context of their environment, for example, to cytokines and extracellular matrix (ECM), and thus we need to move on from *in vitro* to more physiologically relevant and controllable environments that more closely resemble those *in vivo*, aided by the use of various bioengineering solutions such as scaffolds and bioreactors. Current bioengineering is not completely satisfactory – for example, bone grafts are very difficult to connect to the vascular network; they sometimes require bone to be taken from another part of the

body, causing local damage to the site of explantation; and they are very difficult to shape correctly.

Alternative bioengineering solutions: 'naked' decellularised bone and hydroxyapatite-silk fibrin composites were presented. She described their potential to grow both bone and cartilage in one system, by interfacing a hydrogel containing chondrocytes on top of a mineralised scaffold with mesenchymal stem cells (hMSCs) which is under perfusion and then mechanically loaded. Gordana stated that they had obtained between 11-12% mineralisation by culturing hMSCs in the silk scaffold. She reported that this was relatively poor compared to normal bone, but does resemble very osteoporotic bone, and demonstrates the osteogenic ability of hydroxyapatite to differentiate hMSCs, from bone marrow or adipose tissue, to produce bone without the need of growth factors (GFs). Gordana stated that the rate of perfusion is also important, with the optimal perfusion rate $\sim 800 \mu\text{m}/\text{sec}$, which is close to the physiological rate of perfusion. Finally, the architecture of the scaffold was also shown to be important, with smaller pores in the scaffold producing bone resembling flat bones, which are found for example in the skull, and larger pores producing more trabecular-like bones. Flow patterns were also shown to dictate bone morphology. Using various animal studies, Gordana demonstrated the ability of bioengineered scaffold tissues to heal flat bone and trabecular bone defects in a nude mouse and rat models respectively, significantly better than various controls.

Other advantages of these scaffolds were also emphasised. For example, some vascularisation has been observed using these bioengineered scaffolds. The use of 3D imaging was also highlighted, allowing these scaffolds to be exactly shaped according to the patient. These are two problems that still plague current conventional treatments. Prof. Vunjack-Novakovic finished her presentation by reiterating that conditions inspired by the *in vivo* environment were necessary to utilise the full regenerative properties of stem cells. It is possible to not only to create viable, composite and functional tissue grafts, but to also create custom tissues grafts, something

especially important for craniofacial tissue engineering where everybody's face is unique and thus a custom tissue graft can not only improve physical function of a body part, but also improve the psychological well-being of the patient undergoing treatment.

The second presentation was given by **Dr. Jos Malda** (UMC Utrecht, Netherlands) on '*Bioprinting Approach for Regenerative Medicine; Towards an Osteochondral Implant?*' Dr. Malda began by introducing his research area looking at osteochondral grafts. He stated that cartilage is made up of chondrocytes which reside in various distinct zones, each with a distinct function and so different matrix constituents can be found in these different zones. To mimic the different layers of cartilage, his team decided to utilise a bioprinting approach using a 3D fibre deposition (3DF) technique, allowing for computer-controlled precision to 'print' various 3D constructs using cells isolated from the different zones of cartilage and various biomaterials, including the use of thermo-responsive and photo-responsive polymers. Dr. Malda went on to describe various 3D constructs and patterns they had created and their relative efficacy in inducing differentiation and dedifferentiation gene markers. He highlighted the challenge of deciphering what need there is for dictated organisation and whether it's crucial to be in a micrometre scale or whether a millimetre scale is sufficient. Dr. Malda closed by reiterating that as it possible to dictate the layered structure of these constructs, it will be possible to determine the need for interaction between various zones and constituents.

The third presentation was given by **Dr. Blandine Poulet** (Royal Veterinary College, London) on '*Subchondral bone thickening, with or without articular cartilage lesions, in response to joint loading*'. Dr. Poulet began her presentation by highlighting osteoarthritis as a disease of multiple tissues, and that in addition to degeneration of articular cartilage (AC), the underlying subchondral bone (SCB) has also been shown to be thickened, leading to chicken or the egg paradox of which comes first, with evidence of both – AC degeneration or SCB thickening? A murine model was used to explore the relationship and interactions between mechanical loading and genetics using mice from different

genetic backgrounds. In these experiments, non-invasive *in vivo* mechanical loading of 9N was performed on the right knee of the mice 3 times a week for various time periods. Micro-CT scanning was performed on the left (non-loaded) and right (loaded) knee joints with SCB thickness measured. SCB thickness was significantly increased after 5 weeks of loading in the lateral femur, with SCB thickening co-localising with AC lesions, suggesting SCB thickening occurs in response to loading immediately below AC lesions. In the lateral tibia however, there were no AC lesions but some SCB thickening after 5 weeks of loading, suggesting SCB thickening is not down to AC lesions alone. SCB thickness was also more prominent in the most posterior region of the lateral tibia, corresponding to the area which is most compressed during loading, suggesting SCB thickening is as a result of mechanical loading. In conclusion, changes in SCB thickness are induced by mechanical loading independently of AC lesions, but AC lesions can enhance load-induced SCB thickening.

The final talk in this session was by **Prof Molly Stevens** (Imperial College London) on '*New biomaterials strategies for orthopaedic tissue engineering*'. Prof. Stevens first demonstrated that simple biomaterials can be used for tissue engineering when used in a clever way. In an early experiment, injection of calcium alginate hydrogel with no GFs or cells under the periosteum of the tibia in rabbit, creating an *in vivo* bioreactor, resulted in the influx and proliferation of cambial cells, resulting in the growth of new bone that can be used for transplantation elsewhere in the body. Replacement of the biomaterial with hyaluronan (HA) containing liposomes which could slowly release Suramin to stop blood-vessel growth, creating an artificial hypoxic environment, resulted in cartilage growth. This demonstrated that simple biomaterials could be used for tissue engineering, and thus Molly posed the question regarding how complicated biomaterials should be, emphasising the need to strike a balance between the simplicity and organisation of the biomaterial and the GFs introduced. Prof. Stevens went on to discuss her lab's current work using bacterial γ -polyglutamic acid (γ -PGA) as a biomaterial with good mineralising potential. Esterifying the side-group could

alter the water-solubility of the γ -PGA and she revealed that benzyl forms of esterified γ -PGA could increase the osteogenicity of hMSCs. She also showed how altering the mechanical properties (with Professor Paul Smith, ETH, Zurich) - by making a film of the polymer, aligning the fibres in the film - could result in an increase in modulus and tensile strength and allow for 'tailoring' of various tissues. Prof. Stevens then discussed the use of inorganic/organic hybrid nanocomposite scaffolds, which are organised to the nanoscale covalent-linkage structure. Phase imaging revealed nicely arranged domains of around 40 nm within this covalently-crossed nanocomposite material. Interestingly, she demonstrated with videos how altering the cross-links could tailor the mechanical properties of the material, ranging from very spongy materials to very tough ones that could take a fair bit of load, highlighting how these materials can be used for various tissues by tailoring the nanoscale structure.

Prof. Stevens then showed data related to the use of strontium ranelate. She outlined that this compound was already approved for human clinical use and that large doses had been shown to strengthen bones and reduce fracture incidence by stabilising osteoblasts and by preventing osteoclast mediated bone resorption. She showed how StronBone™ (strontium substituted bioactive glass) upregulated osteoblasts and downregulated osteoclasts. In a sheep femur model, use of StronBone resulted in stronger, stiffer bones with significantly less soft tissue. Prof. Stevens revealed that they have just received funding for a 68 patient trial, starting soon in the hospitals affiliated with Imperial College.

Prof. Stevens finished by describing how they tracked differentiation and mineralisation over time in live cells via the use of Raman micro-spectroscopy. This provides in-depth analysis over the course of differentiation compared to traditional staining for mineralisation, which only detects the amount of mineral in fixed cells. Raman micro-spectroscopy can detect the level of crystallinity. Using this technique with traditional methods, the biomechanics of *in vitro* bone formation can be used to further elucidate and characterise cell-source-specific materials used to engineer bone.

Session 2 - Cartilage

Chaired by Prof Anthony Hollander (Bristol) and Dr Emma Blain (Cardiff), the afternoon session opened with a change to the plenary speaker timetable with **Dr. Chris Murphy** (Imperial College London) kindly stepping in to give a presentation entitled '*Hypoxia – A Force for Good in Cartilage*' as Prof Michael Buschmann (Montreal, Canada) unfortunately had to cancel his talk on '*Therapeutic technologies using natural polymers*' due to illness. Dr. Murphy began by highlighting the importance of AC hypoxia, at least in larger animals due to a lack of vasculature, stating that AC uses this hypoxic state to regulate cartilage-specific gene regulation. He went on to highlight the importance of AC in near-frictionless movement of load-bearing joints. Dr. Murphy stated that SOX9 is the main tissue-specific transcription factor that regulates these matrix genes for cartilage-specific function.

Dr. Murphy then elaborated on various factors that drive cartilage-specific gene expression, including mechanical loading, GFs such as TGF β and BMP family members, and finally hypoxia. He showed that in human cartilage explants, a physiologically relevant oxygen tension (1-3% O₂) upregulated COL2A1, Aggrecan and SOX9 mRNA, compared to non physiological oxygen tension (20% O₂). He presented an overview of the Hypoxia-Inducible Factor (HIF) pathway and demonstrated via siRNA knockdown that HIF-2 α and not HIF-1 α was responsible for hypoxia-induced SOX9 upregulation, and in turn expression of type II collagen in isolated human chondrocytes. HIF proteins themselves are regulated via prolyl hydroxylase domain (PHD) proteins, with depletion of PHDs resulting in stabilisation of the HIF proteins. It was shown via siRNA that PHD2 depletion enhanced HIF levels in both normoxic and hypoxic conditions and that this depletion of PHD2 upregulates SOX9, with greater upregulation at 1% O₂ tension.

Dr. Murphy then went on to discuss the anti-catabolic effects of hypoxia, demonstrating that culturing human cartilage explants in hypoxia results in less cartilage matrix protein degradation and also inhibits IL-1 α -mediated aggrecan degradation. Chris then explored the role of HIFs in this anti-catabolic effect,

demonstrating an upregulation of tissue inhibitor of metalloproteinase (TIMP)-3, a chondroprotective protein known to inhibit matrix metalloproteinases (MMPs) and aggrecanases, during hypoxia and showed that this upregulation of TIMP-3 is HIF-1 α -dependent and not HIF-2 α -dependent. Hypoxia was shown to downregulate MMP13, with inhibition of HIF-1 α upregulating MMP13. Dr. Murphy concluded his talk by reiterating that the anabolic effects of hypoxia are driven by HIF-2 α , which regulates SOX9 expression, and in turn cartilage-specific gene expression. Since both HIF-1 α and HIF-2 α are stabilised by inhibition of PHD2, PHD2 inhibition may represent a means of inducing both cartilage repair and protection in large animals. Murine cartilage may not be hypoxic because it is thinner - only a few cells thick – and although avascular may not be regulated in the same way as in larger animals.

The second presentation was given by PhD student **Steven Woods** (Newcastle) on '*miR324-5p in Osteoarthritis and Indian Hedgehog Signalling*'. He began his talk by giving an overview of microRNAs (miRNAs) and how they inhibit gene expression by targeting mRNA for degradation. He stated that due to imperfect base-pairing one gene can be targeted by many miRNAs. He went on to describe previous work in which murine Dicer, an important enzyme involved in the processing of miRNAs from their premature state, had been deleted in all cells expressing type II collagen, and how this resulted in high post-natal mortality and reduced skeletal size and enlarged hypertrophic regions. He also describe another paper in which miR140 deletion in mice lead to OA, but resulted in a far less severe phenotype compared to the conditional dicer knockout, indicating that other miRNAs may function in cartilage homeostasis. By screening miRNAs via RT-PCR Steven discovered miR324-5p upregulation in OA compared to healthy cartilage. He demonstrated how miR324-5p targeted Gli1, a transcription factor involved in the Hedgehog (Hh) signalling pathway. In a luciferase reporter assay, co-transfection of Gli1 3'-UTR with miR324-5p in SW1353 human chondrosarcoma cells resulted in a decrease of luciferase activity, which was rescued by mutating the binding site on the Gli1 3'-UTR, indicating a direct interaction

between miR324-5p and Gli1. In another experiment, addition of miR324-5p to BMP2- and *Ihh*-stimulated C3H10T1/2 murine MSCs abrogated an increase of alkaline phosphatase levels, a marker of chondrocyte hypertrophy and bone formation, suggesting miR324-5p inhibits hypertrophy and bone formation via *Ihh*-Gli1 in OA.

To investigate other potential targets, a SILAC (stable isotope labelling with amino acids in cell culture) proteomics approach was taken. Thus, cells were either labelled with heavy amino acids or unlabelled and subsequently treated with miR324-5p or a control miRNA respectively, and their lysates mixed. A decrease in protein expression in the heavy labelled cells compared to the non-labelled cells would indicate which genes may be targeted by miR324-5p. This was cross-referenced with various 3'-UTR target prediction algorithms to resolve new potential novel targets for miR324-5p, which will be validated by further luciferase assays. Mr. Woods concluded his talk by reiterating that miR324-5p is upregulated during OA and has been shown to be involved in the inhibition of the *Ihh* pathway, an important pathway during OA, and that miR324-5p may also target various other genes.

The final presentation of the session was given by **Prof Susan Chubinskaya** (Rush University, Chicago) on '*BMP-7 in cartilage repair*'. Prof. Chubinskaya provided an overview of cartilage repair, stating that newly synthesised cartilage is more susceptible to re-injury compared to mature cartilage. She mentioned that the bone morphogenetic protein (BMP) family has been extensively studied in this area but that BMP-7 is the most potent family member in different types of human cell culture; overcoming the effect of catabolic cytokines in the presence and absence of serum. BMP-7 knockdown by siRNA was shown to inhibit proteoglycan and aggrecan synthesis. Treatment of chondrocytes with BMP-7 for 48 hours, however, upregulated the expression of various chondrocyte-specific genes, and these were downregulated by siBMP-7. Interestingly, co-treatment with insulin-like growth factor (IGF-1) and BMP-7 provoked greater increases in proliferation and matrix deposition. Blocking BMP-7 in human

chondrocytes also blocked IGF-1 and IGFR expression, with an increase in MMP-13 expression. Similarly, stimulation with BMP-7 upregulated IGF-1/IGFR expression and various other genes implicated in IGF signalling and cell cycle genes. This suggests that BMP-7 restores responses to IGF-1 which are lost with aging chondrocytes. Co-culture of these two growth factors in autologous chondrocyte implantation (ACI) chondrocytes promoted cell survival when grown in culture, which die overtime in culture without IGF-1 and BMP-7. Co-treatment did not increase proteoglycan deposition. Using an acute cartilage trauma method for *ex vivo* modelling, Prof. Chubinskaya noted cell death by necrosis in the area immediately below injury with the rest of the cells remaining viable. Cell death by apoptosis and matrix degradation were also observed in the early phase. At a later stage, anabolic responses included activation of superficial zone protein and autocrine BMP-7. If left untreated, with time, cell death expanded beyond the area of trauma. Treatment with BMP-7 prevented expansion of cell death and improved tissue integrity, as measured by proteoglycan staining, with its stage of action coinciding with the anabolic stage of the untreated explants.

Prof. Chubinskaya finished her talk by discussing further work using a similar trauma-induced OA model *in vivo* in various animal models including sheep, goats and rabbits. Interestingly in an osteochondral defect model in goats, there was an autocrine production of BMP-7 in response to both trauma alone and treatment with exogenous BMP-7, as detected by antibodies against the mature form of BMP-7 used in the treatment, and the pro- form of BMP-7 produced endogenously by the cell. Similar responses were also found in various other animal models. Prof. Chubinskaya concluded that BMP-7 has both pro-anabolic and anti-catabolic effects on cartilage, stimulating tissue repair and degeneration after trauma, improving cartilage integrity, inducing autocrine BMP-7 signalling, preventing the effects of pro-catabolic cytokines and preventing trauma-induced cell-death expansion. This therefore makes BMP-7 a key target in OA.

The first day closed with the **BSMB Fell Muir Award** being awarded to **Professor Bruce Caterson** (Cardiff University) for his continued work on GAG biology, sponsored by the *International Journal of Experimental Pathology*. The start of Prof. Caterson's talk on '**The Glycobiology of GAGs: fun for a few but a headache for some**' was unfortunately plagued by technical issues. When Prof. Caterson was able to resume, he highlighted that extra cellular matrix is important in a number of processes ranging from metabolism to motion and motility, pointing out that if you were to remove all ECM from your body; the rest of your cells would fit into two pint glasses. Prof. Caterson stated that as modifications to the extra cellular matrix cost energy, they must have an importance. He went on to mention the sheer structural diversity of GAG modifications, with the function of many to bind to glycan binding proteins (GBPs) such as growth factors and chemokines, highlighting that there are around 4000 different combinations of GAGs through various linkages, α or β conformations, sulphation patterns, disaccharide composition, etc. Prof. Caterson entertained the floor by demonstrating various different combinations of chondroitin sulphates on his presentation slides using children's toy Duplo blocks aided by a cuddly toy koala bear acting as growth factors.

Prof. Caterson also spoke about the use of monoclonal antibodies to detect specific GAG chains. He demonstrated the ability of these monoclonal antibodies by showing toluidine blue staining of human embryos, staining the anlagen blue due to the presence of chondroitin sulphate (CS). Using monoclonal antibodies against specific GAG chains, Prof. Caterson was able to highlight specific areas of the cartilage matrix, for example, only cartilage that would go on to develop into articular cartilage rather than the rest of the developing growth plate. Antibody staining patterns were also shown to change during the stages of development, illustrating the dynamic changes of CS epitope turnover during development, which would ordinarily be hidden using standard toluidine blue or alcian blue staining. Prof. Caterson also described collaborations with other labs looking at various types of stem cells,

demonstrating a change in CS-antibody staining with maturing stem cell populations, suggesting the surrounding proteoglycan matrix may protect these stem cell niches from the influence of cytokines, etc., that are binding to other GAG chains, creating GBP gradients necessary for cellular differentiation and proliferation during normal tissue development and in repair/regeneration.

Session 3 - Tendons and Ligaments

Chaired by Prof Roger Smith (Royal Veterinary College) and Dr Hazel Screen (Queen Mary, London). the second day opened with a talk from **Prof Butler** (University of Cincinnati, USA) on normal matrix function and structure in tendon and ligament. An introduction centred on the statistics of tendon and ligament injuries, the cost of rotator cuff surgeries (>250 K) and anterior cruciate ligament (75K-125K), as well as their limited success (15-20% for the anterior cruciate ligament). The beginning of his talk explained the difference between different tissues and forces that are placed upon them during daily activities, stressing that ligament show a lower failure force than tendons. This was followed by a focus on the damage incurred by tendons and ligaments during ageing, which reduces biomechanical integrity (rabbit lose 25% of tendon strength between 1 and 4 years of age) and tendon fibril diameter; possibly due to the increased type V collagen (which regulates type I collagen). Ageing tendons are sensitive to loading, show reduced stiffness and a 50% reduction in thickness, area and compressive modulus. There is a substantial reduction in GAG content as well as a 200% increase in permeability. Professor Butler posed the following questions: Does tendon naturally heal? What are the patterns of gene and protein expression? Are cells migrating into wound sites? Using data from both rabbit and Col1-Col2 transgenic murine models, the talk was concluded with current work on improving natural healing with collagen-based matrices augmented with mesenchymal progenitor cells and mechanical stimulation in culture. Future work would focus on development, possible stem cell populations, growth control and how to achieve successful repair.

A second presentation by **Miss Jones** (East Anglia, Norwich) focused on the regulation of matrix components in tendinopathies. Studies in both the Achilles and rotator cuff tendon have shown disruptions of ECM homeostasis in disease (increase in proteoglycans, matrix turnover, type III collagen) and in particular an increase of TGF β expression. Her study focused on analysing the effects of cyclic strain and TGF β stimulation on protease and ECM protein expression by human tenocytes. Analysis in vitro by qPCR, a luciferase assay and gelatin zymography showed patterns of strain response in a large range of genes, mirrored with TGF β stimulation. It was shown that activation of TGF β was increased with strain but not mRNA expression. The talk then focused on finding the mechanism that transforms latent TGF β to active TGF β . A series of genes and signalling pathways were investigated including MMP inhibitors, RGD inhibitors, serine proteases and calcium signalling but to no avail. She concluded that cell-cell contact is important in mechano-transduction and that strain regulates certain proteases and matrix genes. The role of TGF β was highlighted while its mechanism and role in disease remains to be discovered.

The third talk by **Dr Dudhia** (Royal Veterinary College) focused on the fate of mesenchymal stem cells in repair of tendon injuries of the equine forelimb. MSCs have already been used in this way but cell survival was found to be low 3-4 months after implantation. The aim of his work was to promote retention of MSCs in tendon after intra-lesional and intravenous injections. A clinical study of horses 21 days after onset was performed by randomised administration routes (regional perfusion, intravenous and intra-lesional). Although only 2.7-22.5% of cells remained labelled, this was sufficient to continue the study. Cell persistence was shown to be at only 10% within tendons after 24 hours after intra-lesional injections. Intravenous injection showed even less detectable cells in the tendon. However, regional perfusion shows a significant labelling of the tendon. It was concluded that although the optimal number of cells effective in regenerative treatment is not known, the highest cell numbers were found after intra-lesion injections. It was concluded that regional perfusion could be a alternative in the absence of core lesions.

For the last presentation of the session, **Prof Kadler** gave an excellent and engaging presentation highlighting new and exciting findings, decorated by some fascinating images. The precise content of this presentation has been withheld on the author's request.

Session 4 - BSMB Open Session

This was chaired by Prof Tim Hardingham (University of Manchester) and Dr Che Connon (Reading University). **Prof Clemens A. Van Blitterswijk** (University of Twente, Netherlands) opened the BSMB Open Session by giving a talk entitled 'Building complex tissue'. He started his talk by illustrating the complexity of tissue structure and summarised major achievements in understanding this 'complexity' in the last decade: using the example of 'biological effects of ions (Sr²⁺, Cu²⁺, Ca²⁺, F²⁻) for tissue instruction'. Clinical trials data showed that bone tissue engineering have huge individual variation. Prof Blitterswijk showed results of fully synthetic implants based on calcium phosphate ceramic with variable structural and physicochemical characteristics. They were at least equally successful as autografts and rhBMP-2 treatment in the management of a critical-sized bone defects. The data showed that the ability of ceramics to instruct cell and tissue development can be controlled merely by changing either the chemical composition or structural properties.

Surface topography has been widely recognised as a parameter to endow materials with bio-active surfaces. Professor Blitterswijk introduced a high-throughput screening platform for bio-active surface topographies 'TopoChip' which converged high content bio-imaging technology, typically used for screening of biologically active small molecules with micro- and nano-imprint technologies. Prof Blitterswijk described a novel thin-walled 3D chip-type micro-device formed by "microthermoforming" technology, used in engineering artificial cellular microenvironments or niches in film-based multiwall assays, which made it possible to design and assemble structures prone to tissue remodelling, predict and manipulate those developmental mechanisms in vitro, thus create more complex tissue in the future.

The second presentation was given by **Dr.**

Cleo Bonnet (Cardiff University) on the topic of 'Intra-articular AMPA/kainate glutamate receptor antagonists alleviate inflammation, pain and pathology in rat antigen induced arthritis'. Concentrations of glutamate are greatly increased in synovial fluids of RA and OA patients. Dr. Bonnet's study investigated whether the specific glutamate receptor subunits expressed in arthritic synovium could be therapeutically targeted to reduce disease progression and pain. By using the mono-articular antigen induced arthritis (AIA) model, the team used intra-articular injection of NBQX to inhibit AMPA/kainate receptors at the time of arthritis induction, prior to peak IL-6 levels. Over a 21 day period, reduced swelling with pain-related behaviour was found in NBQX-treated rats. Metabo- and iono-tropic GluRs mRNA were differentially expressed in cartilage, synovium, meniscus, fat pad, patella, femoral head and shaft. The results showed intra-articular NBQX can alleviate inflammation, pain and pathology in arthritis in vivo and support the hypothesis that kainate GluRs may be specifically targeted to ease pain, inflammation and pathology in arthritis.

The third presentation was given by Dr. **Ma'an Al-Abbasi** (University of Bristol) entitled 'Changes in collagen cross-linking in human intervertebral disc: with advancing age and severe disc degeneration'. His study was designed to investigate the changes and differences in cross-links (hydroxylysyl-pyridinoline, HL-Pyr; hydroxylysionorleucine, HLNL and pentosidine) associated with ageing and pathological. Intervertebral discs were obtained from seven individuals aged 63-90 years. The data showed a decrease in mature cross-link (HL-Pyr) and an increase in both intermediate (HLNL) and pentosidine cross-link levels with advancing disc degeneration when compared with non-degenerate regions of the same discs. This may represent an increase in matrix turnover. Data were presented to show that mature and intermediate cross-links decline in both non- and degenerating regions with advancing age. Pentosidine showed little difference across the discs, but did show the expected age-related increase. Dr. Al-Abbasi indicated that the increase in pentosidine may be due to the resistance of glycosylated collagen to enzymatic degradation, thus

accumulating with age and becoming enriched as the remaining collagen is lost. He hypothesised that the newly deposited collagen is deficient and that the residual pentosidine levels further contribute to loss of disc integrity and function by increasing its stiffness and reducing elasticity, leading to a mechanically less stable disc.

The fourth talk by **Ms. Jennifer Bara** (Keele University) entitled 'Equine mesenchymal stem cells lose their angiogenic properties when differentiated toward chondrogenic and osteogenic lineages', highlighted a major challenge in osteochondral tissue engineering to promote vascularisation of bone and prevent vascularisation of cartilage. Ms. Bara presented her study on the angiogenic/anti-angiogenic properties of equine bone marrow derived mesenchymal stem cells (eBMSCs) before and after chondrogenic and osteogenic differentiation *in vitro*. The data showed production of angiogenic/angiostatic factors by eBMSCs decreased with chondrogenic and osteogenic differentiation. Endothelial cell tube formation significantly decreased when treated with conditioned media from chondrogenic and osteogenic eBMSC cultures, but in contrast, was promoted by conditioned media from monolayer eBMSC cultures. This suggests that eBMSCs can support angiogenesis *in vitro* and produce an array of angiogenic proteins. Chondrogenic and osteogenic eBMSCs can produce soluble factors that inhibit angiogenesis *in vitro*. Ms. Bara pointed out the balance of angiogenic factor production in differentiated cells may be of concern for osteochondral tissue engineering. Endothelial cell viability/proliferation assays should be used to investigate the mechanism of inhibition by differentiated cells in future.

The fifth talk was given by **Mr. Philip Jones** (Keele University) entitled 'Influence of small proteoglycans on nerve growth in the intervertebral disc'. This examined the roles TGF- β 1 and decorin, a small proteoglycan, in nerve growth regulation. By using chick dorsal root ganglions as a model, the data showed that strips of decorin dose-dependantly inhibited neurite growth (10-500ug/ml). Philip reported decorin inhibition was reversed by chondroitinase ABC treatment, but not AC, and neurite growth

was not significantly affected by TGF- β 1 either solely or in conjunction with decorin. This suggests that dermatan sulphate plays a role in the regulation of nerve growth by decorin. TGF-beta1 had no effect on neurite growth using this model system.

The final talk of this session was given by **Dr. Siyuan Li** (Cardiff University) entitled 'Beta-xylosides inhibition of chondroitin sulphate substitution on matrix proteoglycans perturbs the differentiation of bone marrow stem cells into a chondrogenic lineage'. Chondroitin sulphate (CS) sulphation motifs on cell-associated proteoglycans (PGs) have been shown to be putative biomarkers of progenitor/stem cell sub-populations. They are supposed to play important roles in stem cell differentiation in development as CSs are also found in putative stem/progenitor cell niches at sites of incipient articular cartilage and other musculoskeletal tissues. Dr. Li outlined investigations into the importance of CS in bone marrow stem cell differentiation into chondrogenic phenotype using p-nitrophenyl xyloside (PNPX) as a competitive inhibitor of CS substitution on matrix PGs. DMMB assay showed an apparent delay in cell bead formation in BMSCs cultured with PNPX, indicating a delay in chondrogenesis. Moreover, PNPX significantly inhibited/delayed expression of chondrogenic markers including aggrecan, SOX-9 & type II collagen gene and/or protein expression. Further, IHC analyses showed decreased native CS sulphation epitope expression the presence of PNPX. Dr. Li concluded by highlighting the importance of CSs' role in allowing the chondrogenic differentiation to occur. The precise mechanism is still unclear, but CS sulphation motifs may be involved in the growth factor presentation needed for cell differentiation that leads to cell aggregation and extracellular matrix-cell interactions during chondrogenesis.

Session 5 - Skeletal and cardiac muscle

In this session chaired by Dr Philippa Hulley (University of Oxford) and Dr Sarah Howat (King's College London), **Prof Doris Taylor** (University of Minnesota, USA) opened with a Skype presentation entitled 'Building matrix based solutions for disease: an update'. She began with a review of current cell therapy along the progression of ischemic heart

disease (IHD) and pointed out that one hope of regenerative medicine is to treat underlying tissue damage at the level of the injury, rather than simply mitigating the effects of damage. Decellularization of donor organs such as heart, liver, and lung can provide a naturally occurring 3-dimensional biologic scaffold material that provides perfusion and biologic structural cues that can drive cell behaviour.

Complex interplay between cells, their microenvironments and the vascular network are all critical drivers of myocyte physiology and function. Prof Taylor's group and their collaborators evaluated these in the decellularized organ constructs to explore new opportunities to dissect true potential for repair. Firstly, Prof Taylor's group showed it is possible to rebuild/recell a vascular network with membrane ECs, in both small and large diameter vessels and endocardium, with the function of clot formation inhibition and eNOS expression. Then, she discussed the impact of matrix on stem or progenitor cell alignment, differentiation, function, and physiology as well as its use as an in vitro test bed to evaluate stem cell repair. Her team found in vivo DECELL matrix patches may partially prevent functional decline in fractured hearts. She also showed that cardiac derived PCs changed morphology and gene expression profiles based on matrix source. Evaluation of the matrix architecture, composition and source on stem cell commitment, differentiation and maturation are still underway. Prof Taylor concluded that whole-organ tissue engineering is a potential breakthrough in vascularised tissue engineering, with an ability to leapfrog the current approaches with synthetic biomaterial and their associated obstacles. However, it is important not to claim victory prematurely and create overoptimistic expectations until indisputable success in animal models with organ failure is demonstrated.

The second talk of this session was given by **Dr. Yuxin Cui** (University of Bristol) entitled 'A new methodological sequence to expand and transdifferentiate in vitro human cord blood derived CD133+ cells into cells with a cardiomyocyte-like phenotype'. Stem cell transplantation for human cardiovascular diseases such as myocardial infarction needs to be supported by experimental studies that

allow refinement of the procedure. Dr. Cui reviewed his work on the optimization of a method for the expansion and subsequent differentiation of UCB derived CD133+ stem cells into a cardiomyocyte-like lineage. Immunomagnetic separated CD133+ cells were expanded and differentiated in a novel culture medium that involves sequential signalling factors. Expanded UCB CD133+ cells showed a cardiomyocyte-like phenotype following differentiation in vitro through expressing intracellular cardiac specific markers including cardiac-specific alpha-actin, myosin heavy chain and troponin I. These changes in phenotype are associated with expression of cardiac-specific transcription factors Gata-4 and MEF2C. In addition, changes in phenotype were associated with upregulation of nuclear receptor transcription factors including peroxisome proliferator-activated receptor (PPAR-alpha), PPAR-gamma and retinoid X receptor. Dr. Cui indicated that it is possible to derive cardiomyogenic-like cells from UCB CD133+ stem cells. Further studies should be focused on functional acquisition and cytokine secretion of the differentiated cells. This will permit a more robust manipulation of these cells towards better engraftment and repair in patients with myocardial infarction.

Mr. Stirling Yiin (University of Bristol) then gave a short talk entitled 'Notch Signalling in human induced pluripotent stem cells'. In human embryonic stem cells, Notch signalling is required for the formation of the three primitive germ layers and inhibition of Notch results in a maintenance of pluripotency. Mr. Yiin presented his study of this pathway conducted on human induced pluripotent stem cells (iPSCs). The human iPSC colonies and embryoid bodies (EBs) were analysed for the expression of pluripotency, Notch signalling and germ layer markers genes, in the presence or absence of a gamma-secretase inhibitor (DAPT). The data demonstrated the presence of Notch variants, its ligands and effector downstream genes in human iPSCs. Expression of these genes increased in EBs, suggesting a role for Notch during differentiation. The inhibition of Notch effector genes in EBs by DAPT led to downregulation of all differentiation markers, indicating that Notch inhibition maintains iPSC pluripotency and their differentiation.

The final talk of this session was given by **Dr. Jennifer Morgan** (UCL Institute of Child Health) entitled 'Stem cells and skeletal muscle regeneration'. Dr. Morgan updated the concept of stem cell with a highlight on satellite cells - the stem cells within skeletal muscle, which mediate the skeletal muscle repair, maintenance and regeneration. These cells may become activated in response to muscle injury and proliferate to create a pool of muscle precursor cells that express myogenic regulatory factors and differentiate into postmitotic multinucleated muscle fibres. In vitro and in vivo studies showed that satellite cells are able to regenerate skeletal muscle and functionally reconstitute the satellite cell pool. Normal satellite cells grafted into muscles of the dystrophin-deficient mdx mouse, a model for Duchene muscular dystrophy, undergo little regeneration or self-renewal. But in the prior irradiated host muscle group, donor satellite cells contribute to significantly more muscle fibres. Irradiation incapacitates host satellite cells, but has no obvious effect on either the muscle fibres themselves, or the extracellular matrix. If the host muscle is injured by chemical or physical means that destroy the muscle architecture, donor satellite cell engraftment is not augmented. This result indicated the host muscle environment has a profound influence on satellite cell function. Dr. Morgan indicated that satellite cells are a potential therapy to repair or replace muscle fibres that are lost as a result of ageing, or muscular dystrophies based on the results that young donor-derived satellite cells regenerate and self-renew equally well in young as in mature adult mdx nu/nu mice after pre-irradiation. But satellite cells are not systemically-deliverable and their capacity to regenerate skeletal muscle is reduced by even a short time in tissue culture. Another experiment had showed that other postnatal stem cells, e.g. pericytes, or CD33+ cells, may contribute to muscle regeneration after systemic delivery in animal models of muscular dystrophies. Finally, Dr. Morgan pointed out that the identity of the optimal muscle stem cell, which can be cultured without losing stem cell properties, delivered systemically and give rise to significant numbers of muscle fibres and satellite cells, still remains elusive.

Poster prize winners

Mr Siyuan Li, "Beta-xylosides inhibition of chondroitin sulphate substitution on matrix proteoglycans pertubs the differentiation of bone marrow stem cells into a chondrogenic lineage". Connective Tissue Biology Laboratories, Cardiff University, Cardiff CF10 3AX. E-mail: lis8@cf.ac.uk

Ms Sian Morgan, "Extracellular matrix alterations in wounded mice corneas". Structural Biophysics Group, Cardiff University, Cardiff CF24 4LU. Email: morgansr3@cardiff.ac.uk

Mr Steven Woods, "miR-324-5p in osteoarthritis and indian hedgehog signalling". Musculoskeletal Research Group, Newcastle University, Newcastle upon Tyne NE2 4HH. Email: Steven.woods@ncl.ac.uk

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Ms Eleanor Jones (Student Representative, University of East Anglia; Eleanor.R.Jones@uea.ac.uk)

Welcome to New Members!

We welcome the following new members and student members to the BSMB

Dr Josephine Adams (Bristol); Dr Nandita Singh (Bristol); Dr Riaz Akhtar (Manchester); Dr Ben Walton (Liverpool); Dr Helen McCarthy (RJA Orthopaedic Hospital); Dr Jinju Chen (QMUL, London); Dr Silvia Goldoni (Imperial College, London); Dr Janet Patterson-Kane (Glasgow); Dr Sheona Drummond (Manchester); Dr Cecile Bascoul-Colombo (Cardiff); Dr Karina Wright (RJA Orthopaedic Hospital); Dr Marta Radwan (Newcastle).

Student members:

Jennifer Heyes (Manchester); Sara Dunn (Sheffield); David Wilkinson (Newcastle); Basim Al shamari (Imperial College London); Clare Thompson (QMUL, London); Louise Walkin (Manchester); Vicky Young (Edinburgh); Andreas Heil (Cardiff); James Foster (Reading); Lea Bauer (Cardiff); Elizabeth Shedden (East Anglia).

We hope you all find membership of the BSMB to be enjoyable and rewarding.

Obituary: John Chapman January 2011

John Chapman was a pioneer of the use of electron microscopy for the study of connective tissue. In 1961, when the total number of papers published on collagen was just 223 (compared to 7758 in 2010!), John published his first paper in the *Journal of Biophysical and Biochemical Cytology* (now *Journal of Cell Biology*). Entitled "Morphological and chemical studies of collagen formation", this paper turned out to be remarkably prescient, as the following extract reveals: "In vitro studies on the precipitation of fibrils from solutions of collagen (Nageotte, 1927) have focused attention on the later stages of development and have led to the suggestion that the cell secretes monomeric collagen which aggregates into fibrils in the medium of the extracellular space (Gross et al., 1955; Fitton Jackson, 1956). The mechanism in the living tissue is unlikely to be as simple as this."

Who could have imagined at the time the enormous amount of research activity that would follow over the course of the next 50 years! Then only one type of collagen was known, and the identification of the soluble procollagen precursor was a further ten years away. Now we know that a whole host of non-collagenous molecules are involved in this process. But John was there at the outset, which was typical of the man, who went on to make a number of highly original and important contributions to the field. Trained as a physicist, like many who were attracted to biology at the time, John was concerned with the detail, and was never happier than when putting forward a new hypothesis. His map showing the correlation of the band pattern of collagen fibrils with the amino acid sequence is forever etched in the memory of many of us in the field, and was the forerunner of the many complex maps of collagen interaction sites that have since appeared. Always fascinated by the applications of electron microscopy to matrix biology, he was a pioneer in the development of scanning transmission electron microscopy to study the mass distribution along growing collagen fibrils. His mica sandwich technique is now one of the most widely used for

preparing samples for rotary shadowing. Finally, his review on collagen fibril formation published in 1996 is probably the most cited in the field.

John took great pride in his scientific writing, occasionally consulting 'Fowler's Use of Modern English' about the use of hyphens and when it was acceptable to use a split infinitive. The outcome was a collection of superb manuscripts on collagen fibril structure and assembly that are a joy to read. He had a special gift for expressing complex biophysical concepts in simple, beautifully-crafted English, that few others have been able to emulate. The quality of his writing reflected the clarity of thought and linear thinking that made John a respected and revered scientist.

John was an inspirational figure to many of us, not only for his scientific rigour but also for his larger than life character. Always full of energy and an excellent teacher, he never failed to leave his mark, whether in lectures or at conferences, where his distinctive laugh penetrated late night meetings with friends and colleagues. Many of his research students went on to pursue research careers with great distinction and today follow their mentor's skills in training and developing the careers of young researchers. John had many interests, notably his love for the great outdoors that would often take him to exotic locations such as the Karakoram on the Pakistan/Afghanistan frontier, the subject of a BBC documentary in 1976. Even there his passion for medical biophysics was put to good use, insofar as he was able to identify the probable cause of the endemic goitre in the region as iodine depletion due to binding to mineral phases in the water supply. Such adventures never failed to catch the imagination of fellow scientists, some of whom were lucky enough to take part. So much so that John was often as much in demand for talking about his trekking activities as about his research. Though less exotic, visions of John bounding up Pavey Ark in the Lake District during a lab outing in early 80s are indelibly etched in our memory, and epitomize his unbounded enthusiasm and energy.

John's work as a medical biophysicist was a very important component of research focus at the University of Manchester that began in the 1950/1960s when a small group of basic scientists and clinicians became interested in connective tissues. At the time this was very difficult work and of interest to few biologists except rheumatologists. However, based on the expertise and experience of John and his colleagues over the years, there is now a major international research centre for matrix research in Manchester with over 120 researchers, those early investigations having proved to be relevant to so many areas of biology and medicine.

John was an outstanding scientist and human being, the likes of whom are few and far between. He will be sadly missed, though his voice continues to ring out in our memories.

David Hulmes
David Holmes
Mike Grant
Karl Kadler

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