

Connective Issues

BSMB Newsletter

British Society for Matrix Biology

Committee: Prof. Tim Hardingham (Chairman), Dr Rose Maciewicz (Secretary), Dr. Jay Dudhia (Treasurer),
Dr Jo Lewthwaite, Dr Louise McKenna, Dr Garry Rucklidge, Dr Ian Clark, Dr. Anthony Day, Dr. Alison Reith

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Editorial

by Rose Maciewicz

Welcome to the 54rd edition of Connective Issues our second newsletter as the renamed British Society for Matrix Biology. You will find in this newsletter all the information (Programme, Registration form, Bursary application form and travel directions) pertaining to the Autumn BSMB-BATS meeting in Aberdeen. This meeting will take place on Monday and Tuesday, 6th and 7th September 1999. Please note that the registration, abstract and bursary deadline is Monday July 26th 1999.

Many thanks to Professor Malcolm Davies, University of Wales, Cardiff and the European Tissue Repair Society for organising a tremendous meeting in Oxford this Spring. For those of you who could not attend, a report of this meeting and that of our Annual General meeting, with the 1998 financial report, can be found in this newsletter. Congratulations are also in order to L. Ashworth, S. Wall and C.J. Caunt who were the winners of the IJEP poster competition.

The Committee would like to report that Dr. Ian Clark of University of East Anglia has won our Inaugural BSMB **Young Investigator Award**. We are planning to have this as an annual event and details of the next competition are published in this Connective Issue and can also be found on our website. The next award will be presented at the Spring BSMB meeting in London on Wednesday 31st March 2000 and deadline for receipt of application is October 1st 1999.

The BSMB Committee is pleased to announce that we awarded 3 Bursaries to attend the BSMB meeting in Oxford. The recipients were: Dr. Steve Fenwick (Rheumatology Research Unit, Addenbrookes Hospital); Dr. David Young (School of Biological Sciences, University of East Anglia); and Mr. Mark Baugh (University Division of Children's Health, Sheffield Childrens Hospital). The Secretary would like to thank these individuals for writing the meeting report.

Please make a note in you diaries of the Spring 2000 BSMB meeting, which will take place in London from Monday 3rd April to Tuesday 4th, April 2000. More information about this meeting, including the preliminary programme, can be found within the Newsletter.

The BSMB Committee would like to thank our outgoing Honorary Treasurer Prof. John Gallagher (Patterson Institute, Manchester) for all his diligent work over the last six years and also welcome Jay Dudhia (The Royal Veterinary College, London) to this position. The Committee would also like to thank our outgoing committee members Dr. Alvin Kwan (University of Wales, Cardiff), Prof. Malcolm Davies (University of Wales, Cardiff) and Prof. Jo Edwards (UCH Medical School, London) for their hard work over the last three years. We welcome Dr. Ian Clark (University of East Anglia, Norwich, Oxford), Dr. Anthony Day (University of Oxford) and Dr. Alison Reith (Bergen University, Norway) to the BSMB Committee.

If anyone has items for inclusion in the next newsletter or website, these should be e-mailed or posted to Dr. Rose Maciewicz at the address on the cover page.

Finally don't forget to check our website which can be accessed via <http://www.bsmb.ac.uk>. Between Newsletters all new information received by the Society can be found at the site.

Current BSMB Committee

Officers:

Chairman, Prof. Tim Hardingham (University of Manchester; tharding@fs1.scg.man.ac.uk)
Honorary Treasurer, Dr. Jay Dudhia (The Royal Veterinary College, London; jdudhia@rvc.ac.uk)
Honorary Secretary Dr. Rose Maciewicz (AstraZeneca Pharmaceuticals; rose.maciewicz@alderley.zeneca.com)

Elected Members:

Dr. Garry Rucklidge (Rowett Research Institute, Aberdeen; gjr@rri.sari.ac.uk)
Dr. Jo Lewthwaite (Eastman Dental Institute, UCL, J.Lewthwaite@eastman.ucl.ac.uk)
Dr. Ian Clark (University of East Anglia; i.clark@uea.ac.uk)
Dr. Anthony Day (University of Oxford; AJDay@Bioch.ox.ac.uk)
Dr. Alison Reith (University of Bergen, Norway alisonreith@pki.ubi.no)

ex officio Member:

Dr. Louise McKenna (University Erlangen, Germany; 'Louise.McKenna@patho.med.uni-erlangen.de')

Connective Issues. A copy of the application form is included on page ix of the appended section of the newsletter.

MEMORIA for Dr. Jacqueline Betty Weiss 1926-1999 by Shirley Ayad

It is with great sadness that I write to tell you of the death of Dr. Jacqueline Weiss on the 8th of April, after losing her battle against cancer. Jacky had a long, varied and distinguished scientific career, culminating in the award of the D.Sc. degree. She started her career as a research technician and was subsequently appointed Research Fellow at the Courtauld Institute Middlesex Hospital. She moved to Manchester in 1963 and became a Senior Lecturer in Biochemistry in 1971. Her major research interests have focused on the enzymes involved in collagen degradation and on the factors which stimulate angiogenesis. Although Jacky "retired" in 1993, she continued her research in the Department of Rheumatology at Hope Hospital and remained dedicated to the end, attending the North West Vascular Biology Group Meeting only two weeks before her death.

Jacky once told me that she was expelled from school but she was never a rebel without a cause: in recent years, she gave her time unstintingly to the research association for the blistering disease epidermolysis bullosa (D.E.B.R.A.). This was the real Jacky: beneath her often formidable exterior was a kind, generous lady with a heart of gold, always a champion for the underdog. I was very privileged to have Jacky as both mentor and friend. Jacky was truly a "one-off" and will be sadly missed.

New Organisations of Interest to members of the BSMB

BSMB members might be interested in two new groups 'Action for Biomaterials' Group and the Tissue and Cell Engineering Society. Information about 'Action for Biomaterials' can be found at <http://www.biomaterials-partnership.org.uk/>

For further information on the Tissue and Cell Engineering Society please contact Dr. Julia Polak at j.polack@rpms.ac.uk.

Encourage your colleagues to join the BSMB!

The BSMB can only exist with the support of its members. Please encourage your students, and colleagues, both clinical and non-clinical, to join us. Membership offers reduced registration to all BSMB Meetings, the opportunity to apply for student bursaries and free subscription to our newsletter

BSMB Bursaries for Aberdeen meeting

We are offering BSMB bursaries to attend the Autumn 1999 BSMB meeting in Aberdeen. Young members of the Society are encouraged to apply for bursaries (up to a maximum of £75) to assist with attending these meetings. An application form is included with this newsletter. Bursaries will only be considered if they are submitted on a current BSMB Bursary application form. Applications should be sent to the Secretary and not to the meeting organiser. **The application should be accompanied by a copy of the abstract to be presented at the meeting and a one page curriculum vitae.**

The deadline for receipt of bursaries to attend the Oxford meeting is July 26th 1999. The applications will be reviewed rapidly by the Committee and applicants will be informed of the outcome on or around 15th August 1999.

Criteria for Bursaries

1. Applicants should have been members of the Society for at least 1 full calendar year.
2. Applicants should be submitting an abstract and presenting a poster for the meeting to be attended.
3. Applicants should be at an early stage of their career (i.e. < 5 years from award of PhD) and unlikely to have access to travel funds. Most often where support for an overseas meeting is given this is the first such meeting they attend. For this reason emphasis is always given to young researchers who are generally in short term contract positions, i.e. mainly graduate students and occasionally early post-docs. In addition the Committee will also take into account whether the applicant has received support from the BSMB within the last two years.
4. The work described in the abstract must be novel and likely to be of a quality that would reflect well as a BSMB supported contribution.

BSMB Young Investigator Award

This award aims to recognise the contribution made by younger researchers to the field of matrix biology. The recipient will be invited to give a special seminar at the spring meeting of the Society and will be awarded a one hundred pound honorarium and presented with a certificate. The

cost of attending the meeting will be met by the Society including registration, reasonable travel costs, accommodation and meals. The closing date for receipt of applications is 1st October 1999 and should be sent to BSMB secretary.

Guidelines for applicants for BSMB Young Investigator Award

1. The applicant should be 35 years or under on the date of the presentation of the award.
2. The applicant should have been a member of the Society for at least 12 calendar months.
3. The applicant should apply in writing to the secretary of the Society providing a letter (1 side of A4) stating why they should be considered for the award; a 1 page CV; and a supporting letter from their head of department. The applicant should send one copy of the publication that they think definitively describes the research they have carried out in the field of matrix biology.
4. A committee of four (BSMB Chairman, BSMB Secretary and 2 co-opted BSMB members) will review the application and decide on a winner.

Veterinary Investigation Award

Veterinarians who are active in laboratory-based research in matrix biology are invited to submit applications for this award. Submit your application to the Meeting organisers (Professor M. Bayliss, Royal Veterinary College, Department of Veterinary Basic Sciences, Royal College Street, London, NW1 0TU). The deadline for application is 31st October 1999. Applications will be sent for independent review by the meeting organisers, and the recipient will be invited to give a special seminar at the meeting and will be awarded a two hundred pound honorarium and presented with a certificate. The cost of attending the meeting will be met by the Society including registration, reasonable travel costs, accommodation and meals.

Guidelines for applicants for Veterinary Investigator Award

1. The applicant should be 40 years or under on the date of the presentation of the award.
2. The applicant should apply in writing providing four copies of the following: a letter (1 side of A4) stating why they should be considered for the award; a 1 page CV; and a supporting letter from their head of department. The applicant should send four copies of the one publication that they think definitively describes the research they have carried out in the field of matrix biology.

IJEP Visiting Research Fellowship Scheme

The International Journal of Experimental Pathology is considering applications for the 1999-2000 awards for their Visiting Fellowship Scheme. Full details of the scheme are published in the April issue of the IJEP Journal. The closing date for the application is 30th June 1999.

Spring 2000 BSMB meeting in London - The Millennium Meeting

The Spring 2000 BSMB meeting '**Molecular Cell Biology of the Synovial Joint**' will take place in London from Monday April 3rd to Tuesday 4th, 2000. It will be held at the Royal Veterinary College, University of London, at the Camden Campus of the College. The organisers of the meeting are Professor Michael Bayliss (0171-468 5268, Fax: 0171-388 1027, mbyliss@rvc.ac.uk) and Dr. Jay Dudhia (0171-468 5269, Fax: 0171-388 1027, jdudhia@rvc.ac.uk). The provisional programme for the Meeting follows. As you will not, in addition to the plenary speakers, a number of authors submitting abstracts will be selected by the organising committee to give short presentations of their work and there will be 2 further special talks – one for the **BSMB Young Investigator Award**, and the second for a **Veterinary Investigation Award**. Some of the sponsorship for this meeting will be from Veterinary research funding bodies and from pharmaceuticals with a major interest in Veterinary medicine, and therefore the second award will be supported by these sources.

British Society for Matrix Biology Year 2000 Millennium Meeting

Molecular Cell Biology of the Synovial Joint

Spring Meeting

The Royal Veterinary College, London

3-4 April 2000

Professor Mike Bayliss and Dr Jay Dudhia

Monday 3rd April

10.30 - 1.05 Registration, lunch and poster set-up

1.05 - 1.15 Welcome and Introduction

Bone and Cartilage

1.15 - 1.55 Professor Lance Lanyon

'The responses of bone cells to biochemical and biomechanical stimuli'

1.55 – 2.35 Professor Klaus von der Mark
'Parathyroid hormone/type X collagen: Their role in the mineralization of cartilage'

2.35 – 3.20 *Three 15 minute presentations to be selected from abstracts submitted*

3.20 - 3.50 Tea/Coffee

3.50 – 4.30 Professor Peter Roughley
'Ageing changes in the biochemistry of articular cartilage'

4.30 – 5.00 **BSMB AGM**

5.00 – 6.30 **Poster Session and Refreshments**

7.00 for 7.30 Conference Dinner

Venue possibly at The London Zoo

Tuesday 4th April

Synovium, and Vasculature

9.00 -9.40 Professor Roger Mason
'Biochemical and biophysical properties of the synovium'

9.40 - 10.20 Professor Jo Edwards
'Where do synovial stromal cells come from?'

10.20 - 10.50 Coffee

10.50 – 11.35 *Three 15 minute presentations to be selected from abstracts submitted*

11.35 – 12.05 **Young Investigator Award**

12.05 - 1.30 **Lunch**

1.30 – 2.10 Professor David Blake
'Rheumatoid synovium, the microvasculature and oxidative stress'

2.10 – 2.50 Dr. Peter Winlove
'Microvasculature exchange in the nutrition of cartilage'

2.50 - 3.20 Tea

Tendon

3.20 – 4.00 Dr. Kate Vogel
'Differentiation of tendon tissue'

4.00 – 4.30 Veterinary Award Talk

End of Meeting

Other meeting announcements

The XVIIth Meeting of the Federation of the European Connective Tissue Societies

(FECTS) will be held in Patras Greece on July 1-5, 2000. The BSMB Secretary has been sent a few of the first announcements and will be happy to send one to whoever requests one from her. Note however, all the information can be found on their comprehensive website: <http://www.chemistry.upatras.gr/fects/Index.html>

The Chairman of this meeting is C.Tsiganos, +30-61-997154; constiganos@chemistry.upatras.gr. The Scientific Secretary is N. Karamanos (+30-61-997153; N.K.Karamanos@upatras.gr). Correspondence concerning the meeting should be addressed the Organising Secretariat: Erasmus Horison Ltd, FECTS erasmhor@athena.compulink.gr or erasmhor@

The Biology of Thrombospondins and Other Modulatory Extracellular Matrix Proteins

June 4th-8th, 2000, Memorial Union, University of Wisconsin, Madison, WI, USA. *ORGANISERS* : Deane Mosher, University of Wisconsin and Josephine Adams, University College London

Platform Sessions and Discussions will cover

- **Modulation of Angiogenesis** - animal models, tumor biology, Type 1 Spondin family proteins and other angiogenic regulators
- **Cellular and Molecular Mechanisms** - matrix assembly, protein complexes, receptors, adhesion, cytoskeleton, signaling, cell behavior
- **Protein structure, folding and post-translational processing**
- **Tenascin Family proteins**
- **Matricellular proteins of the Extracellular Matrix** - (SPARC, osteopontin, vitronectin, bone sialoprotein)
- **Tissue Functions** - human diseases, animal and cell culture models)

The meeting will also include Short Talks selected from Abstracts, Poster Sessions and a Trade Exhibit. To join the mailing list, or for comments or questions, contact: dfmosher@facstaff.wisc.edu or dmcbjca@ucl.ac.uk Registration Information available by Web in Winter 1999 <http://www.wisc.edu/union/info/conf/>)

POSTGRADUATE or POSTDOCTORAL RESEARCH SCIENTIST

A research scientist is sought, at postdoctoral or postgraduate level, under a *European Union 'Training & Mobility of Researchers'* grant. The project concerns regulation of hyaluronan secretion into joint fluid, macromolecular sieving by the joint lining (polymer retention), role of cell-matrix interactions in joint lining permeability, and polymer-polymer interactions as factors in joint fluid retention. Trans-synovial transport is fundamental to joint health and to clinical tests of joint disease activity. The project uniquely combines physiological perfusion techniques *in vivo* (animal knee model) with biochemical and biophysical analyses of joint fluid macromolecules (e.g. hyaluronan by HPLC), and offers acquisition of diverse technical experience, with training.

The project is supervised by Prof. JR Levick as part of a collaborative Network of 6 European laboratories studying related aspects of fluid & interstitial matrix physiology/biophysics. The other groups are Profs. Miserocchi & Negrini (Milan, Italy; pleural space, lung microcirculation), Prof Rippe (Lund, Sweden; peritoneal space), Profs Aukland and Reed (Bergen, Norway; b-integrins, interstitial fluids), Prof. McHale (Belfast, N. Ireland; lymphatic electrophysiology) and Prof Michel & Dr Winlove (Imperial Col., UK; capillary and artery wall permeability). The Network aims to advance knowledge of the structure and function of the interstitial matrix; of interstitial body cavities (pleura, joints, peritoneum); of microvascular-interstitial exchange in lung, kidney & mesentery; of lymph formation; and of the electrophysiology of lymphatic smooth muscle.

Candidates should have a good primary university degree, or a PhD, in Physiology or related areas such as Medicine, Biochemistry, Biophysics, Biology, Bioengineering. Due to European Union regulations, only non-UK, European citizens under 35 are eligible. The post is for 3 year (post-doctoral) or, in case of a postgraduate, initially 2 years with possibility of extension by over 1 year.

A successful applicant, if postgraduate, will be encouraged to work towards a higher research degree. The successful applicant will also have the opportunity of an extended visit to another European laboratory in the Network, plus regular, shorter Network meetings at various European locations.

Starting date as soon as possible. Salary according to national university standards plus London Allowance. For a detailed information pack and application form contact The Personnel Officer, address and telephone as below. General information about the TMR programme is on the EU-server, <http://lwww.cordis.lultmr/src/network.htm>.

To apply, write or telephone *The Personnel Officer, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, U.K.* (tel. from outside UK 0044 181 725 5020) and quote reference 203/99.

Report on the BIRAS-BSMB Meeting, London Febuary by Adrian Moore

In vivo models of inflammation and matrix remodelling: classical to modern approaches - A joint symposium between the British Inflammation Research Association and the British Society for Matrix Biology, Saint Bartholomew's Hospital, 25 February 1999.

This meeting was put together in a period of just over 2 months. The speakers were confirmed with less than a month to go and there were very real fears that the short notice would result in poor attendance. Those fears proved groundless, underlying the importance of *in vivo* modelling to the study of inflammation and matrix remodelling. The meeting was deliberately wide in scope stressing the need for refined inflammatory models such as experimental pleurisy in rats (models which lend themselves to all manner of morphological, biochemical and molecular biological techniques) and newer models allowing, for example, the effects of specific gene transfer to be assessed.

Working for more than four decades in inflammation research, Professor Derek Willoughby (Experimental Pathology, St. Bartholomew's & Royal London Schools of Medicine & Dentistry) was asked to take a retrospective look at his career and share in some of its achievements. He started by describing pleural models of inflammation and how these had been used to define a role for mediators released early in the inflammatory response. It was shown that a sequential release of mediators occurred (vasoactive amines, kinins and prostanoids) irrespective of the initiating stimulus. These studies were followed by the demonstration of a role for complement in models such as carrageenan pleurisy and thermal injury. This challenged the prevailing view that complement activation occurred solely as a result of antigen/antibody complexes. A crude extract of lymph nodes, termed lymph node permeability factor (LNPF) was shown capable of duplicating the pathology of delayed type hypersensitivity (DTH) reactions and antibodies to LNPF suppressed models of DTH. We would now recognise many of the attributes of LNPF to be due to the presence of Th1 cytokines. The immunology theme continued with scanning electron microscopy showing for the first time antigen presentation by macrophages to lymphocytes. The bridges formed between these cells and the molecular interactions involved remain an important area of research today. Time and again we were reminded as to how much progress has been made in the last 40 years. For example, the origin of macrophages in inflammatory lesions was thought to be the fibroblast! Simple labelling

of blood monocytes indicated the true origin of the macrophage and led to the realisation that granulomatous inflammation could be maintained by continued cell migration or local proliferation- important when deciding which model to use in assessing, for example, agents that inhibit cell accumulation. The effects of granulomatous inflammation on cartilage degradation was described with the importance of assessing inflammatory changes separately from matrix integrity. The animal models predicted that certain non-steroidal antiinflammatory drugs might be detrimental to cartilage. The work was then brought up-to-date with summaries of work currently being undertaken in the areas of angiogenesis, inducible enzymes and apoptosis. Finally, Professor Willoughby was generous in acknowledging his collaborators over the years, the list reading rather like a Who's Who in inflammation research.

Dr Dean Willis (Experimental Pathology, St. Bartholomew's & Royal London Schools of Medicine & Dentistry) introduced the stress response as an adaptation to an inflammatory insult. In acute pleural models of inflammation in the rat he developed the hypothesis that the adaptation to stress was an important aspect in bringing about resolution of the inflammatory response. As an example, he showed how hsp32, an inducible form of the enzyme heme oxygenase, was maximally expressed in terms of protein expression and enzymic activity in cell pellets harvested from carrageenan inflammatory exudates at 48 hours, a time when the inflammatory response was waning. Inducing increased hsp32 activity 24 hours into the inflammatory response was markedly anti-inflammatory whereas inhibition was proinflammatory. Using tissue homogenates containing both nitric oxide synthase (NOS) and heme oxygenase, treatments that inhibit NOS were shown to increase heme oxygenase activity. These treatments were without effect in homogenates containing heme oxygenase but low levels of NOS. However, nitric oxide donors decreased heme oxygenase activity in both homogenates. The suggestion that NOS and HO may have reciprocal modulatory effects in inflammation has been given further support from studies of the expression of these enzymes in an in vivo model of septic shock. Briefly, Dr Willis touched on other studies showing induction of hsp70 in inflammation. Curiously, aspirin treatment increased expression of hsp70, perhaps contributing to its anti-inflammatory effects.

Professor Yuti Chernajovsky (formerly of the Kennedy Institute for Rheumatology and recently appointed head of the Bone & Joint Research Unit, St. Bartholomew's & Royal London Schools of Medicine & Dentistry) discussed some of the progress being made to treat inflammatory arthritis using gene therapy. First he stressed some of the advantages of this approach. Switching on a gene in diseased tissue to produce an anti-inflammatory factor should lead to a high local

concentration of the gene product and low systemic levels, the reverse of administering the gene product intravenously. In addition, it is a long term strategy which should not require patients having to attend clinics for multiple treatments. In terms of potential problems, Professor Chernajovsky considered that the use of viral vectors for gene transfer would be a major safety issue to be overcome before the work could progress to man. Exerting control over the administered gene, for example through a tetracycline response element, would effectively allow treatments to be reversible. A number of possible gene constructs were discussed, including genes encoding the soluble TNF receptor, TGFb and soluble CR1. Adoptive transfer of splenocytes from DBA/1 mice with collagen II arthritis to immunodeficient (SCID) mice results in arthritis development. Arthritis development could be blocked if the splenocytes were infected with a retrovirus expressing the soluble p75 TNF receptor or TGFb. Because these transferred cells recognise collagen II (the major cartilage collagen), this is a means of targeting the gene therapy to the joint structures. Isolation of collagen II reactive T cell clones from arthritic patients is however very difficult, but in man targeting of the joint structures may be achieved using T bodies, T cells expressing chimeric receptors composed of a fragment of antibody recognising type II collagen and lymphocyte triggering molecules.

The molecular theme of the meeting was continued by Dr Patricia Sime (Royal Infirmary of Edinburgh). She used an elegant model to study the effects of TNF over expression in lung tissue. TNF expression is up regulated in a number of inflammatory lung conditions where it is associated with fibrogenesis. The possible mechanisms underlying this fibrogenesis were investigated using an adenovirus to transfer cDNA of TNF into rat lung. The vector was chosen because of its ability to target lung epithelial cells and indeed this was where protein was expressed, peaking three days after infection and then waning. This was associated with an accumulation of inflammatory cells, mainly neutrophils and mononuclear cells peaking at about day 7 and thereafter declining. Fibrogenesis (collagen and elastin deposition) became apparent from about day 14. The transient expression of TNF and the temporal disassociation with fibrogenesis suggested that fibrogenesis was through a secondary mediator. Transforming growth factorb (a fibrogenic cytokine) was measured in bronchoalveolar lavage fluid, it's peak coincided with the peak of inflammatory cell infiltration and preceded the onset of fibrogenesis. Using immunocytochemistry to demonstrate alpha smooth muscle actin, a myofibroblast marker, Dr Sime developed a model whereby TNF expression led to accumulation of inflammatory cells and induction of TGFb. This cytokine in turn led to the differentiation of the myofibroblast phenotype which then resulted in fibrogenesis.

Dr Michael Seed (Panceutics) discussed the importance

of angiogenesis to a variety of physiological and pathological processes. In particular the dependence of granulomatous inflammation on new blood vessel growth was stressed together with the concept that inhibition of angiogenesis could halt the invasion of cartilage and bone by rheumatoid pannus. In developing a model to assess the effects of angiostatic agents on granulomatous tissue development a differentiation needs to be made between these agents and agents acting as classical anti-inflammatory drugs. A murine chronic granulomatous air pouch model was described in which carmine is used to form a vascular cast which can be dissected. An index of the tissue dry weight and extracted carmine content gives a measure of vascular density. An angiogenic therapy (oral heparin) and an angiostatic therapy (oral heparin and a sub anti-inflammatory dose of cortisone) indicated that the model responded appropriately. Prior to carmine injection, animals are warmed to dilate the peripheral circulation, in addition, inclusion of gelatin with the carmine prevents leakage of the dye to the tissues. These steps are crucial and explain why injection of vasoactive mediators have no effect on vascular index. The stimulus for angiogenesis in this model appears to result in a vasculature that is more than sufficient to allow granulomatous tissue development. Agents acting to suppress blood vessel development can therefore have a greater effect on carmine content than tissue dry weight and thus reduce vascular density. In a model of granuloma induced cartilage breakdown in the mouse, angiogenic therapy increased matrix loss and angiostatic therapy spared matrix loss, thus providing the first in vivo evidence that cartilage degradation by granulomatous tissue is angiogenesis dependent. Dr Seed then went on to share data from Dr J. Winkler (SmithKline Beecham) both of which dose dependently suppressed angiogenesis in the air pouch model. SB220025 is a selective p38 MAP kinase inhibitor, SB203347 is a secretory PLA₂ inhibitor which was also shown to suppress murine collagen II arthritis.

The next speaker was Dr Philip Hawkins (Immunological Medicine Unit, Royal Post Graduate Medical School, Hammersmith Hospital), who spoke of the problems associated with amyloid deposition. Many proteins have the potential to form amyloid fibrils including monoclonal immunoglobulin light chains, serum amyloid A, prion proteins and lysozyme. Partial protein unfolding can result in proteins adopting a β -pleated sheet conformation that is able to act as a template to bind similarly folded molecules into fibrils. Large amyloid deposits interfere with normal organ function and can prove rapidly fatal. Irrespective of the proteins involved, all amyloid fibrils are capable of binding serum amyloid P. Amyloid deposition is delayed in mice with targeted deletion of the serum amyloid P component. This supports the view that serum amyloid P may stabilise the fibrils and render them relatively resistant to proteolytic attack. The binding of serum amyloid P to amyloid deposits has been exploited by using labelled

serum amyloid P as a tracer substance in patients with systemic amyloidosis. Scintigraphic imaging shows promise as a diagnostic tool and indicated that clinical treatment of systemic amyloidosis can cause regression of amyloid deposits. This demonstrated that amyloid deposition is not necessarily irreversible and that turnover is more dynamic than previously suspected.

Dr. Rose Maciewicz (AstraZeneca Pharmaceuticals) concluded the programme and talked about the use of Imaging modalities to monitor disease progression in animal model and humans. She presented examples of the use of magnetic resonance imaging (MRI), QCT and others in looking at inflammation, extracellular matrix structure and remodelling as well as and blood flow, angiogenesis.

Report on the BSMB-ETRS Meeting, Oxford University, March 31st to April 2nd 1999 by Steve Fenwick, Mark Baugh and David Young

Organizers for BSMB were Dr Robert Steadman and Prof. Malcom Davies (Institute for Renal Disease, UWCM, Cardiff) while those for the ETRS were Professor Keith Harding and Dr Keith Moore (Wound Healing Research Unit, UWCM, Cardiff) and Dr George Cherry (Oxford Wound healing Institute). In total 285 people registered for the meeting representing England, Wales, Scotland, Denmark, Norway, Germany, France, Canada, Israel, Italy, USA, and Sweden

Sponsors for the meeting included THE WELLCOME TRUST, CONVATEC, PFIZER CENTRAL RESEARCH, SMITH NEPHEW, KNOLL AG, BIOWHITTAKER, BLACKWELL, GENZYME, HYBAID, JOHNSON & JOHNSON MEDICAL, CALBIOCHEM-NOVABIOCHEM, DAKO LTD, CORNING COSTAR UK LTD, JANSSEN-CILAG LTD, NYCOMED, AMERSHAM, NOVEX, TCS BIOLOGICALS, YAMANOUCHI, AND CARL ZEISS LTD

The meeting was opened by **Finn Gottrup** (Copenhagen, Denmark) with a talk providing an overview of the clinical aspects of wound healing. He described how wounds in the clinical practice can be assigned into three categories; normal healing, healing with scar complications and delayed or non-healing. With the use of graphic slides (just after lunch) he emphasised to us all the cost both in terms of healthcare and the decrease in the quality of life for patients of wound complications and concluded that further research

is required before the optimal clinical prophylaxis and treatment of wounds can be established.

Richard Clark (New York, USA) discussed the requirements of fibronectin (FN) for cells to migrate from a collagen matrix into a fibrin clot. This migration occurs at day three when cells have concomitantly altered their integrin expression. Cultured cells were able to migrate maximally on a monomer fragment of FN, CHV120, that contains the integrin binding domain (RGD) along with heparin binding and IIICS domains. Modification of this FN fragment to circumvent proteolysis could allow its use as a "smart matrix" to promote healing by decreasing the current 3 day delay in cell migration into the wound.

In the following session **Keith Moore** (Cardiff, Wales) discussed inflammatory cells in wound healing. Besides a role in infected wounds these cells may also play a regulatory role in normal healing, as demonstrated in animal models where impairment of macrophage or T-lymphocyte function delays the healing process. Macrophages, which release cytokines and growth factors, along with MMPs and TIMPs, are not correctly activated in non-healing venous leg ulcers as measured by their deficiency in TNF α secretion. This can be rectified by the addition of LPS. This demonstrates that optimising the inflammatory response through pharmacological modulation may prove beneficial to the healing process.

Alexis Desmoulière (Bordeaux, France) discussed the retractile role of the myofibroblast (granulation tissue fibroblast) in wound healing. Granulation tissue develops during normal wound healing with myofibroblast depositing the majority of the ECM components. Once the wound has fully re-epithelialised the myofibroblasts are removed probably by apoptosis. However, in hypertrophic scars α -smooth muscle actin (α -SMA, a myofibroblast marker) expression remains elevated. TGF β and other growth factors/cytokines increase the expression of α -SMA and therefore may play an important role in myofibroblast dedifferentiation. The converse occurs with γ -IFN or resveratrol (a constituent of flavonoid phenolics found in wine!) which could therefore represent candidate anti-fibrotic "drugs".

In the days second session **Jim McCarthy** (Minneapolis, USA) discussed aspects of work in his laboratory regarding integrin mediated cell

adhesion and motility and its modifications through interactions with cell surface proteoglycans (CS-GAGs), in this case MCSP. MCSP and $\alpha_4\beta_1$ integrin contact one another through CS-GAGs and also bind overlapping domains on fibronectin (FN) which together promotes cell spreading. MCSP clustering induces tyrosine phosphorylation of p130cas via the action of the rho-subfamily GTPase cdc42. He concluded that co-ordinate interaction of cell surface CS-GAGs and specific integrins, in response to ECM components (*i.e.* FN), may be required for signal transduction complexes to form at the cell surface that play a role in cell migration.

Andrew Newby (Bristol, England) spoke about cell matrix interactions in the vascular response to injury. His talk focused upon smooth muscle cell (SMC) migration and proliferation and resultant neo-intima formation. Both *in vivo* and *in vitro* the use of adenovirus-TIMP vectors prevented SMC migration showing that both ECM degradation via MMPs and growth factor action (for SMC proliferation) act co-ordinately yet distinctly in the response to vascular injury. Interesting aspects of his talk included inflammation upregulating MMPs expression via the transcription factor NF-kappa-B and TIMP-3 promoting apoptosis within the neo-intima.

In Sessions **3 Thomas Kreig** (Cologne, Germany) discussed the role of integrin:collagen interactions and also mechanical tension in mediating fibroblast MMP-1 and type I collagen expression. Binding via $\alpha_1\beta_1$ causes a down regulation in type I collagen expression whereas $\alpha_2\beta_1$ integrin binding results in increased MMP-1 production and collagen gel contraction. He also discussed how fibroblasts isolated from patients with the fibrotic disease Scleroderma do not down-regulate collagen production to the same extent as normal fibroblasts when cultured in collagen gels despite expressing normal levels of $\alpha_1\beta_1$ integrins and suggested that there may be alterations in signalling pathways in fibroblasts found in sites of fibrosis.

Giovanni Abatangelo (Padova, Italy) described the importance of hyaluronan as a structural component of the extracellular matrix, its interactions with other ECM molecules and its role in regulating tissue water balance. HA is also capable of protecting cells against free-radicals and is important in development and angiogenesis possibly by reducing cell attachment. He showed recent work where combinations of HA film and HA

wool with keratinocytes have been effective in the treatment of chronic venous leg ulcers.

This session also included a lecture by the recipient of the first IJEP Young Investigator Award, **Ian Clark** (Norwich, England). He discussed his work investigating the structure of the TIMP-1 gene promoter and the different regions involved in constitutive and inducible expression using deletion mutations of exon-1 and intron-1.

In Session 4, **Judith Campisi** (Berkeley, USA) described the causes and potential consequences of cellular senescence. Normally somatic cells do not divide indefinitely and when they have reached the end of their replicative life span they become senescent which involves growth arrest, resistance to apoptotic death and altered phenotype. Cell senescence is caused by the gradual shortening of telomeres that occurs with each cell division and possibly also types of DNA damage or abnormal mitogenic signals. The accumulation of senescent cells with age may be involved in the decline of tissue integrity and function, tumourigenesis and chronic wound healing.

John Savill (Edinburgh, Scotland) discussed the role of ECM molecules in regulating myofibroblast survival in the wound environment. Apoptosis is the major mechanism for the removal of myofibroblasts during cutaneous wound healing. Increased apoptosis may lead to the phagocytosis of apoptotic cells by dendritic cells capable of presenting self antigens and the development of auto-immunity. He described how normal components of the mesangium such as collagen IV and laminin provide survival signals to mesangial cells via non-adhesion dependant mechanisms. In contrast in the scarring mesangium there is an accumulation of type I collagen and serum-type fibronectin which fail to provide survival signals and lead to increased apoptosis of myofibroblastic cells.

William Parks (St. Louis, USA) presented work describing the interaction between MMP-1 and $\alpha_2\beta_1$ integrin. Expression of MMP-1 by keratinocytes is induced by contact with type I collagen and activity of the protease is essential for cell migration. It has previously been shown that MMP-2 may interact with $\alpha_v\beta_3$ on endothelial cells. He showed that the pro domain of proMMP-1 is capable of binding to the I-domain of α_2 at a site separate from that of type I collagen. Binding to the integrin causes activation of the protease without cleavage of the enzyme and may be involved the precise delivery

of the protease to its target substrate and enabling migration across ECM surface.

Leif Lund (Copenhagen, Denmark) discussed the role of plasmin in wound healing. Plasmin is formed by the conversion of plasminogen by the plasminogen activators, tPA and uPA, of which the latter is expressed on migrating keratinocytes. Plasminogen knockout mice are found to develop normally but suffer from spontaneous ulcerations involving reduced wound closure due to a lack of keratinocyte migration.

Session 5 contained presentations of two selected posters, **Derek Mann** from Southampton (England) who discussed his work investigating DNA:protein interactions involved in the sustained induction of TIMP-1 expression in myofibroblastic hepatic stellate cells which are responsible for the deposition of matrix leading to liver fibrosis. The second poster by Steven Wall (Norwich, England) presented evidence showing reduced MMP-2 activity in the wounds of a mouse model of diabetes. Chronic foot ulcers are a common complication in type II diabetes and wounds in *diabetic* mice show delayed reepitheliazation and fibroplasia possibly mediated by cells being unable to detach from the surrounding matrix caused by reduced MMP-2 expression.

Jill Helms (San Francisco, USA) described the involvement of hedgehog proteins in skeletal development and repair. In development Indian hedgehog (Ihh) protein was found to recruit and induce proliferation of cells of the chondrogenic lineage. Application of exogenous Ihh protein into tibial fractures was found to cause increased collagen types II and X expression and also cartilage callus which suggests that exogenous delivery of Ihh may accelerate aspects of fracture repair.

A guest lecture was also given during this session by **Alan Hall** (London, England). He discussed the structural and dynamic roles of filamentous actin and its regulation by GTPases such as Rac, which induces actin formation around the membrane and the generation of lamellipodia, and cdc42, which induces more slender filapodia. Inhibition of GTPase activity caused loss of polarity and lamellipodia leading to a reduction in cell migration caused by alterations in intracellular actin assemblies.

Paul Martin (London, England) gave an overview of his work utilising drosophila and zebrafish embryos as models of embryonic wound healing due to the similarities observed in their mechanisms of wound closure. Embryonic epidermis contract wounds by a GTPase Rho-dependant actinomyosin pursestring method in contrast to adults where epidermis migrate at wound edges by extending lamellipodia. Embryonic wounds also heal without scarring or an inflammatory response and in mice lacking macrophages or functional neutrophils wounds healed more effectively than in wild-type mice.

In Session 6, **Martin Humphries** (Manchester, England) reviewed the structure and function of fibronectin. He discussed the crystallographic structure of fibronectin in relation to its integrin and heparin-binding regions focusing on the HepII domain and in particular focused on the alternatively spliced IIIICS region.

Fiona Watt (London, England) described her work investigating integrin expression by keratinocytes during wound healing. Normally keratinocytes express $\alpha_2\beta_1$, $\alpha_3\beta_1$ and $\alpha_6\beta_4$ integrins and this is restricted to those cells in the underlying basal layer. However during wound healing there is a switch to $\alpha_5\beta_1$ and $\alpha_v\beta_6$ expression which is no longer confined to the basal layer. The significance of this expression was discussed.

To begin Session 7, **Steve Mutsaers** (introduced us to the concept that the mesothelium heals in a different manner to epithelial tissue. He presented two possible theories of where the 'wound healing' cells came from; either the submesothelium or from progenitor cells within the mesothelium itself. Using a model of heat damaged testes, data showed that the submesothelium dies upon injury, yet healing still occurred providing evidence against healing arising from the submesothelium. Incorporation of dye-labelled mesothelial cells into a mesothelial wound in a rat model supported the theory of a mesothelial-derived source of wound healing cells.

Clive Roberts discussed the matrix changes in remodelling lung tissue associated with pulmonary fibrosis and showed that much of the tissue is replaced with a collagen rich matrix. The major interest lay in the type and function of proteoglycan in this process. Regions of fibroblast proliferation were shown to contain high concentrations of GAG and the proteoglycan 'versican'. From mRNA expression, 2 of the 4 known versican variants

were shown to be involved in this pathology. A rat model was also shown. Pneumonia infected rats showed macrophage clearance of fibrotic lesions. The possible roles for versican in lung matrix were summarised.

Charlie Archer (Cardiff) gave an overview of how poor articular cartilage is at repairing and some strategies currently in use to achieve cartilage repair. He showed that areas of cartilage repair break down after the initial healing response, therefore long-term repair does not occur. The hypothesis 'that cartilage repair fails because of cell death around the wound site' was put forward. Two models (chick sternum and bovine articular cartilage) were used to show that chondrocytes around the wound site undergo apoptosis and that there are changes in matrix metabolism around the site, indicating a possible phenotypic drift in the chondrocytes. Evidence was shown that lesions in cartilage filled with either the plug of removed cartilage or agarose containing IGF prevented apoptosis of cells at the wound site. It was therefore hypothesised that apoptosis of chondrocytes bordering the wound site is due to the removal of some factor from the cartilage when damage occurs.

Gillian Ashcroft (Baltimore & Manchester) described a protocol for the measure of rate and quality of wound repair. Human subjects over a wide age range were punch biopsied on the upper arm and healing was assessed histologically. Older subjects showed a lower number of monocytes, higher number of granulocytes, increased activity of MMP-9 and increased staining for CD15 over younger subjects. Healing in the older subjects was slower, however, scar tissue was less pronounced than in younger subjects. The same protocols were performed on patients undergoing HRT and healing was shown to occur in a similar manner to young subjects. Dr Ashcroft concluded that estrogen alters the wound healing response and went on to show how topical applications of estrogen to a rat incision model altered the rate and quality of wound healing.

Sharon O'Kane (Manchester) described a protein called Gelsolin and its role in modulating actin filament formation. She discussed the changes seen in a Gelsolin knockout mouse model and showed that wound collagen deposition, cell migration and re-epithelialisation occurred at a slower rate than in the wild type, concluding that it is an important protein in regulating fibroblast

function. The importance of EGF and its receptor in fibroblast function were also discussed, and how important the binding of decorin to the EGF receptor is. The importance of decorin was shown via a decorin knockout. Wounds in these animals were generally wider and showed delayed re-epithelialisation.

In the final Session, **John D. Williams** (UWCM, Cardiff) highlighted that changes in the peritoneal membrane affect peritoneal dialysis in patients undergoing this treatment for kidney failure. Damage, which generally manifests as acellular regions, occurs through repeated infection and from continuous exposure to dialysis fluid, which is physiologically incompatible with bodily fluids. Lack of a good animal model led to the development of an *in-vitro* model whereby a monolayer of mesothelium is scratched and cell response was examined at the cellular and matrix level. Several growth factors were also tested for their effects on cell proliferation in 3-dimensional culture. Data was provided to show that dialysis fluid from infected patients had a mitogenic effect above and beyond that of non-infected fluid and even 10% serum. This fluid was also shown to cause a change in phenotype in the cells to smooth muscle actin positive cells and there were indications of fibrosis seen as type I collagen deposition.

David W. Thomas (Dental School, UWCM< Cardiff), proposed that the oral mucosa heals without scarring due to excellent re-epithelialisation and organisation of the matrix. The phenotype of the oral mucosal cells was discussed and proposed to be similar to that of foetal fibroblasts. Oral fibroblasts were shown to have an increased production of pro- and active MMP-2 and Scatter Factor (HGF) and were shown to repopulate a 3-D model of wound healing faster when compared to age matched skin fibroblasts. Dr. Thomas emphasised the importance that saliva has in aiding the wound healing process and discussed the problems associated with periodontal wound healing, micro-organisms and drug induced damage.

After proposing that evolution has developed an ineffective wound healing process, designed principally to cope with a surface scratch Gus McGrouther (London) gave an overview of the clinical perspective of surgical wounds and the approach to assessment and treatment of wounds was described. Mr. McGrouther emphasised that there is a difference in the way scientists and

clinicians view a wound. After stating that all wounds heal with the exception of chronic wounds associated with a general disease process, the features of the wound margins and wound bed and some of the controversies in the treatment of a wound were addressed. He briefly mentioned the mechanics of the fibroblast reaction to wounding and demonstrated a 3-D model of fibroblast stretching and their responses to being stretched and stated that scar formation depends on having the correct strain on the forming scar. Concluded that wound healing is generally an excessive process.