

# Connective Issues

## BSMB Newsletter

British Society for Matrix Biology

**Committee:** Prof. Tim Hardingham (Chairman), Dr. Rose Maciewicz (Secretary), Dr. Jay Dudhia (Treasurer),  
Dr. Ian Clark, Dr. Anthony Day, Dr. Alison Reith, Dr. Norman McKie, Prof. Anthony Hollander, Dr. Graham Riley

Registered Charity no. 281399

No. 60 March 2002

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**FECTS 2002  
BRIGHTON UK**

**Note Abstract Deadline and Early Registration is  
March 29<sup>th</sup> 2002.**

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- 6 Spring 2003 BSMB Meeting, Oxford 31<sup>st</sup> March to 1<sup>st</sup> April 'Extracellular Matrix: from Structure to Function'.
- 6 Autumn 2003 BSMB Meeting, London, to mark the retirement of Professor Roger Mason, tentatively 18<sup>th</sup> to 19<sup>th</sup> September 2003,
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**Please send letters, comments or editorial to Dr. Rose Maciewicz**, Respiratory and Inflammation Research Department,  
AstraZeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK  
Tel +44 (0)1625 513231; Fax + 44 (0)1625 510823 or email [rose.maciewicz@astrazeneca.com](mailto:rose.maciewicz@astrazeneca.com)

## Editorial by Rose Maciewicz

Welcome to the 60<sup>th</sup> edition of Connective Issues.

Items for your attention include:

- Preliminary Agenda for BSMB 2002 AGM to be held at FECTS Brighton on July 29<sup>th</sup> 2002.
- Call for XVIIIth FECTS Bursaries.
- Information about the Biochemical Society Meeting, Cardiff, 16<sup>th</sup> to 18<sup>th</sup> July 2002 'Biology of the Intervertebral Disc'
- Dates for the next two BSMB meetings.
- Membership subscriptions for 2002 are due. Please make sure you are a fully paid member and your details are up to date.

Many thanks to Dr. Ian Clark for the organisation of the Autumn 2001 BSMB meeting in Norwich. If you could not attend the meeting a report can be found in this newsletter. Thanks to Emma Blain and Clare Curtis, our two Bursary recipients for writing the meeting report.

Don't forget to check our website regularly (<http://www.bsmb.ac.uk>). Between Newsletters all new information received by the Society can be found at the site.

See you all at the FECTS meeting in Brighton.

## Current BSMB Committee

### Officers:

Chairman, Prof. Tim Hardingham (University of Manchester; [timothy.e.hardingham@man.ac](mailto:timothy.e.hardingham@man.ac))  
Honorary Treasurer, Dr. Jay Dudhia (The Royal Veterinary College, London; [jdudhia@rvc.ac.uk](mailto:jdudhia@rvc.ac.uk))  
Honorary Secretary Dr. Rose Maciewicz (AstraZeneca Pharmaceuticals; [rose.maciewicz@astrazeneca.com](mailto:rose.maciewicz@astrazeneca.com))

### Elected Members:

Dr. Ian Clark (University of East Anglia [clark@uea.ac.uk](mailto:clark@uea.ac.uk))  
Dr. Anthony Day (University of Oxford; [ajday@bioch.ox.ac.uk](mailto:ajday@bioch.ox.ac.uk))  
Dr. Alison Reith (University of Glasgow,) [ar113r@clinmed.gla.ac.uk](mailto:ar113r@clinmed.gla.ac.uk)  
Dr. Norman McKie (Medical School, University Newcastle-upon-Tyne; [nmckie@hgmp.mrc.ac.uk](mailto:nmckie@hgmp.mrc.ac.uk))  
Prof. Anthony Hollander (University of Bristol Medical School; [a.hollander@bristol.ac.uk](mailto:a.hollander@bristol.ac.uk))

Dr. Graham Riley (Soft Tissue Injury and Repair Group, Addenbrookes Hospital [gpr1003@cus.cam.ac.uk](mailto:gpr1003@cus.cam.ac.uk))

### Co-opted Members:

Two BSMB members have been co-opted onto the committee to help with the organisation of the XVIIIth FECTS and are:

Dr. Jo Lewthwaite (The Royal Veterinary College, London; [jlewthwaite@rvc.ac.uk](mailto:jlewthwaite@rvc.ac.uk))

Ms. Katherine Lamb (The Royal Veterinary College, London; [klamb@rvc.ac.uk](mailto:klamb@rvc.ac.uk))

## Call for nominations for BSMB Chairman and Committee Members

The current BSMB Chairman, Professor Tim Hardingham and four Committee Members (Dr. Ian Clark, Dr. Anthony Day, Dr. Alison Reith and Dr. Norman McKie) are due to retire in 2002. Normally the retirement takes place at the AGM. This year will be no different except that the AGM will be held at the FECTS meeting on 29<sup>th</sup> July 2002. The Chairman and all Committee members have agreed to stay on until the end of July. In addition, the Committee proposes that Dr. Anthony Day's retirement is postponed until the AGM in 2003. This will enable him to organise the BSMB Spring 2003 meeting and also decrease the number of Committee members leaving at any one time.

We are therefore looking for nominations for these positions. Please write to the Secretary with suggestions and/or nominations and include the following information:

Name:

Position:

Research Interests:

Qualifications to be Chairman:

**Or**

Why I want to be on the Committee

Note that another BSMB member must second this nomination and for Chairman the nominated person must have been a BSMB Committee Member/Officer at one time.

***Nominations must be received by June 1<sup>st</sup> 2002.*** If required a postal ballot will be held prior to the AGM.

## **Publications of BSMB Meeting Abstracts in International Journal of Experimental Pathology**

The abstracts for the Spring 2001 meeting held at the University of Manchester on April 2<sup>nd</sup> – 3<sup>rd</sup> 2001 on “Cellular and Molecular Mechanisms in Tissue Engineering” are now published and can be found in *Int. J. Exp. Path.* (2001) **82(6):A1-A25**.

The abstracts for the Autumn 2001 meeting of the BSMB, which took place on the 3<sup>rd</sup> – 4<sup>th</sup> September 2001 at the University of Norwich on 'The Impact of Proteinases on Matrix Biology', will be published in *Int. J. Exp. Path.* during 2002.

## **Membership Renewal Information**

The membership fees for 2002 are now due. We are requesting that all members complete the attached form '**Membership Subscription for 2002**', which can be found on the penultimate page of this newsletter. The completed form with membership payment should be forwarded to the BSMB Secretary. The form should be self-explanatory but if you have any queries please contact the Secretary by e-mail.

Note that the 2002 membership fee is £10.00 for full members and £2.00 for student members. As in the past no subscription is payable by Honorary Members.

If you pay by Direct Debit please confirm that your Bank has the correct details, which are as follows:

Account name: British Society for Matrix Biology  
Account Number: 09670343  
Sort Code: 60-00-01  
Branch: NatWest,  
City of London Office,  
PO Box 12258,  
1 Princess Street,  
London EC2R 8PA

If you do not pay by Direct Debit please send us a cheque immediately. Please note that the membership fee is collected on January 1<sup>st</sup> of the year. If you fail to send us your 2002 subscription fee we will have to cancel your membership. Please help the Society to stay solvent by paying your membership fees.

Under the provision of the Data Protection Act 1994 s.33(3) we are required to inform our members that we are holding a mailing list on computer disc. The information is only for the purpose of distributing or recording the distribution of articles of information to members and consists only of their names; addresses and other particulars necessary for such distribution. A member objecting to the information being held as mentioned should notify the current BSMB Secretary.

## **Professor Mike Bayliss: An Announcement**

I am sure that BSMB members will be sorry to hear that Professor Mike Bayliss has been diagnosed with progressive supra-nuclear palsy (PSP), a rare hypokinetic movement condition that has similarities to the more common Parkinson's disease. PSP is not well understood, but is believed to be due to degenerative changes in the basal ganglia. The cause is unknown. Professor Bayliss has asked that this information is made public, as it is unlikely that he will be able to return to full time work again. For more information on PSP, see <http://www.psp.org/>

## **BSMB Website**

The statistics show that the number of visitors to our website has substantially increased over the last year (2001). For example, there were more than 1,000 visitors to the website for the month of December 2001, compared to some 2,000 visitors for January 2002. This will increase further in the coming months with the Brighton FECTS meeting approaching fast, which is all the more reason why members are encouraged to make contributions to place on the website. This can include job advertisers as well as job seekers, articles of interest from your laboratory, reviews on subject areas that our membership (and further afield) may find stimulating. You may want to use the website as a Noticeboard to discuss specific areas that effect research (i.e. as a News Forum). The BSMB Committee would greatly encourage this; you can forward items to the Secretary or to any of the Committee members.

## **XVIIIth FECTS Meeting Brighton, UK 27<sup>th</sup> – 31<sup>st</sup> July 2002**

This year the BSMB are hosting FECTS 2002. Due to the large workload associated with organising this meeting there will be no Spring or Autumn BSMB meetings in 2002. All BSMB members should have received either an email or print copy of the final announcement for FECTS. If you have not, or would like further copies then please email the FECTS Organising Secretary, Jo Lewthwaite (jlewthwaite@rvc.ac.uk). In addition Registration and Abstract Forms can be found at <http://www.bsmb.ac.uk/fects2002>.

We have secured some excellent speakers for the scientific programme including:

### **Sunday - Connective Tissue Disorders and Therapies**

**Ranieri Cancedda** (Genova, Italy): Regeneration & repair of connective tissues: a tissue engineering approach

**Matthias Chiquet** (Berne, Switzerland): Regulation of ECM gene expression by mechanical stress in fibroblasts

**Brendan Lee** (Houston, USA): The role of the transcription factor, CBFA1, in cleidocranial dysplasia

**Leena Bruckner-Tuderman** (Munster, Germany): Mutations in collagen 17 and effect on ECM assembly

### **Monday - Cell Matrix Interactions in Development**

**Kazayuki Sugahara** (Kobe, Japan): Glycosaminoglycan glycosyl transferases differential assembly of sugar backbones of heparan sulphate and chondroitin sulphate on the common linkage region

**Scott Selleck** (Tucson, USA): Heparan sulphate signalling in *Drosophila* development

**Cheryl Tickle** (Dundee, UK): Development of skeletal pattern in vertebrate limbs

**Bjorn Olsen** (Boston, USA): Genetic and cellular control of skeletal development and homeostasis

### **Tuesday - Extracellular matrix cell signalling**

**Agnes Noel** (Liege, Belgium) Membrane type-1 matrix metalloproteinase and TIMP-2 in tumour angiogenesis

**Peter Friedl** (Wurzberg, Germany): Tumour cell migration strategies within 3D ECM

**Amin Arnaout** (Boston, USA): Crystal structure of integrins: twists, turns and signalling.

**John Couchman** (London, UK): Signalling through syndecan-4 and its role in cell-matrix adhesion

### **Wednesday - Matrix Assembly and Turnover**

**Johanna Myllyharju** (Oulu, Finland): Prolyl 4-hydroxylases, the key enzymes of collagen biosynthesis

**Monique Aumailley** (Cologne, Germany) Laminin 5 processing and integration into ECM

**Peter Ekblom** (Lund, Sweden): Regulation of basement membrane assembly by protein kinase B

**Markus Ruegg** (Basel, Switzerland): The role of ECM in synapse formation and neuromuscular disease

The deadline for early registration and abstract submission is 29<sup>th</sup> March 2002. We have established online forms for registration, abstract submission and accommodation booking these are available at our website [www.bsmb.ac.uk/fects2002](http://www.bsmb.ac.uk/fects2002)

## **Annual General Meeting**

The Annual General meeting will be held at the XVIIIth FECTS Meeting in the Brighton Centre, Brighton UK on Monday 29<sup>th</sup> July 2002 at 12:30. The preliminary agenda follows. Additional items for inclusion should be sent to the BSMB Chairman, Professor Tim Hardingham and arrive no later than July 12<sup>th</sup> 2002.

### **Preliminary Agenda**

#### **BRITISH SOCIETY OF MATRIX BIOLOGY ANNUAL GENERAL MEETING**

**29<sup>th</sup> July 2002**

**12:30 – 13:30**

**Brighton Centre, Brighton**

1. Approval of Minutes of the last AGM held in Manchester 2<sup>nd</sup> April 2001, Hulme Hall, University of Manchester
2. Matters Arising
3. Secretary's report
4. Treasurer's report
5. Election of New Chairman
6. AOB

## **BSMB Bursary for FECTS meeting**

We are offering bursaries to attend XVIIIth FECTS. Young members of the Society are encouraged to apply for bursaries (up to a maximum of £300 from the BSMB) to assist with attending this meeting. An application form can be found on page 11 & the Society's website <http://www.bsmb.ac.uk>.

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. **A copy of the abstract to be presented at the meeting and a one-page curriculum vitae should accompany the application.**

**The deadline for receipt of bursaries to attend the meeting is April 15<sup>th</sup> 2002.**

The Committee will review the applications rapidly and applicants will be informed by email by end April.

### **Criteria for Bursaries**

1. Applicants should have been members of the Society for at least 1 full calendar year before the 1<sup>st</sup> day of the meeting for which they are seeking a Bursary.
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.

## **Preliminary Notification**

Biochemical Society Meeting 667  
16-18 July 2002, Cardiff University

**Host Colloquium: *Biology of the Intervertebral Disc***

**Research Colloquium: *Connective Tissue***

This year the Biochemical Society is organising a meeting of general interest to our membership. They are aiming to attract contributions from young researchers working on all aspects of connective tissue. For further information please see the attached circular or contact:

The Meeting Office, Biochemical Society  
59 Portland Place  
London W1B 1QW  
e-mail:meetings@biochemistry.org

Note that the Abstract deadline of 7<sup>th</sup> May 2002 and early registration deadline is 4<sup>th</sup> June 2002.

## **Preliminary Notification**

Spring 2003 BSMB Meeting

St. Catherine's College, Oxford

**"Extracellular matrix: from structure to function"**

The Spring 2003 Meeting of the British Society for Matrix Biology will take place on 31<sup>st</sup> March/1<sup>st</sup> April 2003 at St. Catherine's College, Oxford. The topic of the meeting is "Extracellular matrix: from structure to function" and will contain sessions around Glycosaminoglycan structure/function, Matrix remodelling, Fibrillar structures, Pathogen-matrix interactions and Matrix receptors. The meeting is being organised by Drs. Anthony J. Day, Penny Handford and Helen Mardon. For further details please contact tony.day@bioch.ox.ac.uk.

Please note that the Annual General Meeting of the BSMB (2003) will be held on Monday 31<sup>st</sup> March.

## **Preliminary Notification**

Autumn 2003 BSMB Meeting

Imperial College London

In Autumn 2003 (tentatively 18<sup>th</sup> and 19<sup>th</sup> September), a special BSMB meeting will be held at Imperial College of Science, Technology & Medicine, London to mark the forthcoming retirement of Professor Roger Mason. Roger has been a stalwart of the connective tissue research community for many years, and this meeting will be the ideal opportunity for his many friends and colleagues to extend their best wishes. The meeting will be organised by Professor John Couchman (Imperial College),

and Dr. Graham Riley (Rheumatology Research Unit, Box 194 Addenbrooke's Hospital). Its major theme will be related to the physiology and pathology of kidney. Further information will be available in the next Newsletter.

## **Preliminary Notification**

### **Spring 2004 BSMB Meeting**

#### **University of Bristol**

#### **“Ligament, Bone and Cartilage in Musculoskeletal Disease”**

Advanced notice is given of the BSMB 2004 Spring meeting. This will be held at the University of Bristol and will be organized by Professor Anthony Hollander (a.hollander@bristol.ac.uk). The theme will be “Ligament, bone and cartilage in musculoskeletal disease”. Further information will appear in the next Newsletter.

## **BSMB Meeting Report**

### **Autumn 2001 BSMB Meeting University of East Anglia, Norwich**

#### **“The Impact of Proteinases on Matrix Biology”**

**by Emma Blain and Clare Curtis**

The autumn meeting of the BSMB was held at University of East Anglia, Norwich on 3<sup>rd</sup> –4<sup>th</sup> September 2001 and had as its theme “The Impact of Proteinases on Matrix Biology”. The meeting was organised by Dr. Ian Clark and attracted 112 delegates. Amersham Pharmacia Biotech, Chemicon International, R&D Systems, AstraZeneca Pharmaceuticals and Glaxo SmithKline provided financial support.

For those of you who missed the meeting the clear message from BSMB Norwich: the impact of proteinases in matrix biology is to “keep taking the cod liver oil tablets and drink plenty of green tea” – our joints may then survive the strains of everyday life!

**Dr. Voon Wee Yong (University of Calgary, Canada)** opened the meeting with a plenary lecture on ‘MMPs in the CNS – friend or foe?’. This thought provoking plenary provided ample data to question that MMPs are only involved in pathology. Elevated MMPs in the CNS are associated with e.g. malignant glioma, multiple sclerosis, Alzheimers disease etc suggesting that they are the bad guys. However, in CNS trauma, MMPs may also be the good guys through promoting migration of precursor cells,

degradation of inhibitory matrix, release of growth factors anchored to matrix, axonal elongation etc.

Introducing serine proteases to the meeting, **Dr. Vince Ellis (UEA, Norwich)** discussed the implication of the plasminogen activation system in pericellular proteolytic processes such as migration and invasion in cancer metastasis, various vascular disorders and neurodegenerative diseases such as the transmissible spongiform encephalopathies. The mechanism by which plasminogen, the most abundant zymogen in the body generates plasmin is believed to occur through the binding of the plasminogen activators (PA) to specific cellular receptors. Urokinase PA (uPA) binds to the uPA receptor (uPAR), and tissue PA (tPA) to a recently identified type II membrane protein on vascular smooth muscle cells (shares homology with p63 kinase). The resulting complexes interact with membrane-associated plasminogen to form higher order complexes, which enhance plasminogen activation – suggesting a mechanistic pathway for the activation of this protease system.

Recent studies conducted in Dr Ellis's laboratory have involved the regulation of plasmin generation by abnormal isoforms of the prion protein (PrP). He presented some interesting data indicating that abnormal PrP, but not normal PrP can bind tPA and plasminogen, increasing plasmin production. Abnormal PrP is believed to be devoid of Cu<sup>2+</sup> promoting the induction of increased plasmin activation. Construction of a mutant incorporating a Cu<sup>2+</sup> binding site abolished the PrP's ability to activate plasmin. Studies to be pursued by Dr Ellis and his group include determining whether the binding of tPA is a normal function of PrP i.e. are tPA knockout mice protected from prion infection? He concluded his talk with the idea that as tPA and plasminogen are expressed by neurons in the brain and therefore plasmin may have a role to play in the pathogenesis of neurodegenerative disorders such as prion diseases?

Molecular assembly of MT1-MMP on the cell surface regulates tumour cell invasion – **Dr. Yoshi Itoh (Kennedy Institute for Rheumatology, London)**. Of the six identified membrane type MMPs (MT-MMP), MT1-MMP has an important function in the activation of MMPs -2 and -13, which proceed to activate MMP -9 leading to subsequent matrix breakdown. Dr Itoh presented his studies on the activation of pro-MMP 2 by MT1-MMP with reference to cancer cell invasion – through which they have elucidated the mechanism involved in this activation process. MT1-MMP, present on the cell surface, and bound by TIMP-2 at its active site acts as a receptor for pro-MMP-2. Pro-MMP-2 binds to the C-terminal domain of the TIMP-2, and adjacent TIMP-2-free MT1-MMP molecules activate the pro-MMP-2 in this ternary complex. Via deletion mutants of the MT1-MMP domains, it was discovered that the MT1-MMP forms a homodimeric complex through the hemopexin-like domain (PEX) – its function being to

maintain close proximity between adjacent MT1-MMP molecules to facilitate pro-MMP-2 activation.

Dr Itoh related this recently elucidated the mechanism of activation of pro-MMP-2 by MT1-MMP to that of cancer cell invasion. Dimerisation of the MT1-MMP molecules regulated by cytoskeletal reorganisation is believed to be induced by Rac1; accelerated MT1-MMP dimerisation at the ruffling edge of the membrane enhances pro-MMP-2 activation. Immunolocalisation studies have shown the colocalisation of MT1-MMP and pro-MMP-2 activation in lamellipodia, allowing the migration of tumour cells through the basement membrane. Dr Itoh posed the question of whether endogenous MMP-2 activity could be diminished in these pathological conditions? Studies conducted deleting the PEX domain of MT1-MMP, or replacing it with the PEX domain of MT4-MMP resulted in the abolition of pro-MMP-2 activation at the cell surface. Furthermore, isolated PEX domain has a dominant negative effect on pro-MMP-2 activation.

Recovery from liver fibrosis: matrix degradation and the fate of the hepatic stellate cell – **Prof. John Iredale (University of Southampton)**. With images enough to put off even the hardened drinkers amongst us (!), Prof. Iredale assured us that the hepatic stellate cells (HSC) are indeed equipped with survival strategies, and can reverse the effects of established fibrosis, caused for example by alcohol! HSC respond to injury by excessive secretion of ECM proteins, trans-differentiating into myofibroblast-like cells and proliferating – the pathology of liver fibrosis. In cultured primary hepatic stellate cells, there was decreased collagenase expression and increased TIMP levels. By day 3 of culture, the levels of pro collagen type I increased following on from elevated TIMP-1 suggesting that the fibrotic cells were laying down matrix. These findings have led to the hypothesis that progressive fibrosis results from a failure to initiate matrix degradation.

Although previously viewed as irreversible, Prof. Iredale's use of models of biliary and parenchymal liver injury have demonstrated that the fibrotic process is reversible. Recovery from fibrosis induced by carbon tetrachloride and bile duct ligation occurs over 4-6 weeks following removal of the insult i.e. CCl<sub>4</sub> and bilio-jejunal reanastomosis respectively. Using these models, Prof. Iredale presented data indicating that by day 28 the cells recovering from fibrosis showed decreased levels of collagen type I, TIMP-1 and -2 with parallel increases in MMP-13, in comparison to control levels of untreated liver cells. These changes provide evidence of matrix remodelling. Apoptosis of activated HSC was also evident as a mechanism for their removal on recovery from fibrosis. HSC apoptosis may present a default pathway and which is forestalled during progressive injury because HSC are given survival signals. Apoptosis of activated HSC appears to operate in removing the cells responsible

for neomatrix production. But, do TIMPs mediate hepatic stellate cell survival? Enhanced TIMP activity was detected in surviving HSC, suggesting that TIMP-1 and -2 may act as autocrine survival signals. These reassurances, by a doctor, of reversible liver fibrosis ensured that everyone had a "good time" at the BSMB dinner!

Cell networks and control of MMP 9 and TIMP 1 secretion in tuberculosis – **Dr. Jon Friedland (Imperial College, London)**. Previous talks encompassing the diversity of pathological conditions to which matrix proteases are involved were further exemplified by Dr. Friedland, and his presentation on tuberculosis (TB). TB is characterised by cell recruitment leading to granuloma formation, necrosis and tissue destruction – potentially mediated through MMP-induced leucocyte recruitment and tissue injury. The focus of the talk addressed the point of whether monocyte-derived MMP activity promotes TB. *In vitro* studies conducted on human monocytic cells (THP-1) infected with live, virulent *Mycobacterium tuberculosis* indicated increased secretion of MMP-9 in a dose dependent manner; MMP-9 mRNA was detected as early as 24 hours post infection. Elevation of TIMP 1 was not as profound. *In vivo* analysis of cerebrospinal fluid from TB meningitis patients again demonstrated increased MMP-9 secretion, an increase considerably higher than fluids from bacterial or viral meningitis. The identification, both *in vitro* and *in vivo*, of higher MMP-9 to TIMP-1 concentrations results in a matrix-degrading phenotype. This finding was significant because the increased MMP-9 concentration in cerebrospinal fluid was associated with fatal TB meningitis and cerebral tissue damage, and not severity of systemic illness.

Since very low levels of infection increased MMP secretion, Dr. Friedland inoculated non-infected cells with media from infected monocytes and observed the induction of MMP-9 in the non-infected cells. The possibility of a monocyte-monocyte amplification network potentiated through pro-inflammatory cytokines was tested by blocking select cytokines and analysing MMP-9 expression – a 50% decrease in MMP-9 was observed upon blocking of TNF $\alpha$ , therefore TNF $\alpha$  is instrumental in inducing the MMP-9 driven development of this matrix-degrading phenotype. Minimal effects were noted with T<sub>H</sub>2 cytokines, but T<sub>H</sub>1 cytokines i.e. IFN $\gamma$  abolished the MMP-9 signal. Within 24 hours, IFN $\gamma$  switched off MMP 9 expression suggesting an equally pivotal role for IFN $\gamma$  in the host defence to TB.

Opening the second day's session, **Dr Drew Rowan (University of Newcastle)** discussed the involvement of T cell-derived cytokines in the pathogenesis of rheumatoid arthritis (RA), and their contribution to cartilage breakdown. The work of Dr Rowan's laboratory has focussed on the proinflammatory cytokine IL-17's ability to initiate cartilage collagen degradation. An increased level of

IL-17 has been previously shown to promote loss of proteoglycan and collagen type I from bone and synovium. Experiments presented by Dr Rowan indicated significant release of collagen from bovine nasal cartilage explants by IL-17 in a dose-dependent manner - this effect was attenuated by adding IL-4, IL-13, TGF $\beta$  or IGF-1, inhibiting collagen release by 50-85%. Synergistic effects were observed when IL-17 was combined with IL-1, IL-6 (only in the presence of its soluble receptor sIL-6R), TNF $\alpha$  and oncostatin M (OSM) in inducing collagen degradation. Addition of TIMP-1 or BB-94 (an MMP inhibitor) abolished the release of collagen. IL-17 was shown to induce the expression of MMP -1, -3 and -13, and enhanced MMP expression was detected when IL-17 was combined with the aforementioned pro-inflammatory cytokines. Dr. Rowan's findings demonstrate that IL-17 can by itself, or in combination with TNF $\alpha$ , OSM, IL-1, or IL-6 and IL-6sR promote MMP-mediated cartilage collagen breakdown. All the above pro-inflammatory cytokines are elevated in RA synovial fluid, and, from the data presented, suggests that IL-17 could act as a potent upstream effector of collagen breakdown in inflammatory joint diseases such as RA.

**Clare Curtis (University of Cardiff)** presented data on how *n*-3 polyunsaturated fatty acids can modulate degradative and inflammatory processes in human osteoarthritic cartilage. The data showed that *n*-3 fatty acids and no other class of fatty acid could cause a specific reduction in the activity and expression of aggrecanase and collagenase. Also a loss of expression of inflammatory mediators (cyclooxygenase-2, 5-lipoxygenase, 5-lipoxygenase activating protein, IL-1 $\alpha$ , IL-1 $\beta$  and TNF- $\alpha$ ) was demonstrated in cartilage supplemented with *n*-3 fatty acids whilst genes involved in housekeeping functions (cyclooxygenase-1, 12-lipoxygenase and 15-lipoxygenase) were unaffected by *n*-3 fatty acid supplementation.

**Dr. Chris Little (University of Cardiff)** presented results from studies investigating the catabolism of numerous extracellular matrix molecules associated with the type II collagen fibrils in articular cartilage. Using in vitro models of progressive articular cartilage degeneration the temporal relationship between the catabolism of aggrecan, type II collagen and biglycan, decorin, fibromodulin, type IX collagen and COMP was studied. He demonstrated that following the early aggrecanase generated loss of aggrecan, biglycan was catabolised and released from cartilage prior to late stage MMP-generated type II collagen degradation. All other molecules were released at the same time as the type II collagen. It was suggested that catabolism of biglycan may be a prerequisite for subsequent collagenolysis.

**Dr. Zara Poghosyan (UEA, Norwich)** discussed adamalysin, tyrosine kinases and cell signalling. The data presented showed that the cytoplasmic domains

of a number of the ADAMs can associate with the Src family kinases and that the associations were dependent upon phosphorylation of the ADAM. The data showed that a number of Src family kinase SH3 domains interact with ADAM15 in haematopoietic cells. Phosphorylation of the ADAM increased this interaction whereas dephosphorylation of the ADAM decreased the interaction.

**Dr. Shu Ye (University of Southampton)** discussed polymorphisms in MMP and TIMP genes. The presentation focussed on naturally occurring sequence variants in the genes encoding the MMPs and TIMPs, of which the 5A/6A polymorphism in MMP-3 and the 1G/2G polymorphism in MMP-1 were discussed in detail. Of the 5A/6A polymorphism in the MMP-3 gene promoter, the 5A allele has greater promoter activity than the 6A allele. An association of the 6A allele has been made with progression of atherosclerosis. The 1G/2G polymorphism in the MMP-1 gene results from an insertion (or deletion) of a guanidine at position -1607 in the gene promoter. The GGAT motif created by this polymorphism is a binding site for the Ets family of transcription factors and is also close to an AP-1 site, and it has been demonstrated that the 2G allele has greater transcriptional activity than the 1G allele. The 2G allele is more frequent in patients with ovarian cancer than healthy subjects and has also been associated with increased invasiveness of malignant melanomas. Discussed in less detail were polymorphisms in the MMP-9 promoter and coding region; polymorphisms in the MMP-2 promoter region in a SP-1 consensus element and polymorphisms in the MMP-12 gene promoter that influences an AP-1 site.

**Mark Bond (University of Bristol)** discussed the mechanisms underlying TIMP-3-induced apoptosis. The data demonstrated that the N-terminal domain of TIMP-3 was important in inducing apoptosis. TIMP-3 was able to induce activation of the initiator caspases (8 and 9) and caspase-mediated cleavage of the death substrates FAK and PARP. CrmA and bcl-2 (inhibitors of the caspase 8 and caspase 9 pathways respectively) inhibited TIMP-3 induced apoptosis. Overexpression of a dominant negative FADD also blocked TIMP-3 induced apoptosis, indicating that TIMP-3 induces a type II apoptotic pathway initiated by engagement of the FADD sensitive death receptor. Data was also presented showing that TIMP-3 induced apoptosis was TNF- $\alpha$ , FAS-ligand and TRAIL independent.

**Kevin Leco (University of Western Ontario, Canada)** presented data on the TIMP-3 knockout mouse. The data showed that TIMP-3 deficient mice show air space enlargement in the lung. In aging mice, there is an increase in the mean alveolar size in the lung which effects gaseous exchange ability. It was also shown that the null mice have a decreased abundance of collagen I, an increase in denatured collagen around the bronchioles and disorganised

collagen fibrils in the alveolar interstitium. In the null mice, there did not appear to be any compensation by other TIMP isoforms as there was no upregulation of TIMP-2 or TIMP-4. Using *in situ* zymography an increased MMP activity was shown in the surrounding bronchioles and interstitium of the knockout mice. It was suggested that the deletion of TIMP-3 results in a shift in the MMP/TIMP balance in the lung to favour extracellular matrix degradation. The null mice also showed a slight alteration in the polarity of the implanting embryo, cardiac dilation in aged mice and accelerated apoptosis in the involuting mammary gland.

**BRITISH SOCIETY FOR MATRIX BIOLOGY**  
**BURSARY APPLICATION FORM for XVIIIth FECTS**

**The deadline for receipt of bursaries to attend the meeting is April 15<sup>th</sup> 2002.**

Application form to be completed and returned with

- a copy of the completed Conference application form
- a copy of the abstract to be presented at the meeting
- a one page *curriculum vitae*, to:

BSMB Secretary, Dr Rose Maciewicz, Senior Principal Scientist  
 Respiratory and Inflammation Research Department, AstraZeneca Pharmaceuticals  
 Alderley Park, Macclesfield, Cheshire, SK10 4TG UK

The applicant should have been a member of the British Society for Matrix Biology for 12 months prior to the start date of the meeting for which the bursary application is being applied. Applicants will be informed as soon as possible and should not await such notification before submitting their Conference application.

Name.....Date.....

Address.....  
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e-mail:..... tel:..... fax:.....

Conference Name.....

Venus and Date.....

Costs (accommodation, registration, travel).....

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Additional sources of support (Indicate other sources to which you will apply for financial assistance to attend the Conference and the amount you might expect to receive.)

Support statement (A brief supporting recommendation by the applicant's Head of Department or Supervisor.)

Date.....Name (HOD).....Signature.....

Date.....Signature of Applicant .....

# BRITISH SOCIETY FOR MATRIX BIOLOGY

## MEMBERSHIP APPLICATION FORM

Note an Electronic Copy of this form can be found at <http://www.bsmb.ac.uk>

To be completed in BLOCK CAPITALS. Please include appropriate membership fee. Return to:  
BSMB Secretary, Dr Rose Maciewicz, Respiratory & Inflammation Research Area, AstraZeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG UK. email: [rose.maciewicz@astrazeneca.com](mailto:rose.maciewicz@astrazeneca.com)

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TWO SPONSORING MEMBERS: *Should you not know any member of the Society personally, please write to the Secretary.*

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FEES: Full membership £10 p.a.....Student membership £2 p.a.....(Please indicate with a tick)  
STUDENT MEMBERSHIP (To be signed by the student's supervisor)

I certify that  is a non-salaried research student.

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The application should be accompanied by a cheque, made payable to the BRITISH SOCIETY FOR MATRIX BIOLOGY, for the subscription for the current year January to December. Please complete the banker's order for future subscriptions. Should your application be unsuccessful your cheque and banker's order will be returned.

DO NOT DETACH

### BANKER'S ORDER

To: (name and full address of your bank)

Please pay on the 1st January to **National Westminster Bank plc, City of London Office, PO Box 12258, 1 Princess St., London, WC2R 8PA; Code No. 60-00-01T,**

the sum of £  ( POUNDS, in words) for credit to the account of the BRITISH SOCIETY FOR MATRIX BIOLOGY,

Account No. 09670343 quoting reference no.  (leave blank, for BSMB records only) and make similar payments annually on the 1st January until this order is cancelled in writing, charging such payments to:

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Signature: .....Date.....

# MEMBERSHIP SUBSCRIPTION FOR 2002 ARE NOW DUE - PLEASE COMPLETE AUDIT OF MEMBERSHIP DETAILS

Please fill out the following form, **EVEN IF NONE OF YOUR DETAILS HAVE CHANGED** and return by April 29<sup>th</sup> 2002 to Dr. Rose Maciewicz, Respiratory and Inflammation Research Department, AstraZeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK

In order for the Society to keep accurate records of our membership and those who pay their subscriptions it is necessary for us to ask you to complete these details however they will not be passed onto any 3<sup>rd</sup> party unless you agree to this.

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