# International Society for Matrix Biology Newsletter

**No. 6- May 2007**

## Contents



## From the President's Desk

Dear ISMB members,

In my last letter I wrote to let you know of your Council's vision of Fostering, Connecting and Networking Matrix Biologists World-Wide and promoting Matrix Biology as a key research area linking multiple disciplines. I spoke then of our plans for new initiatives towards achieving this vision. In the past few months your Council has been working hard on several fronts.

**Partnership with the Pan-Pacific Connective Tissue Societies (PPCTS)**
We are happy to announce that, with the generous contribution from the publishers of our journal, *Matrix Biology*, the ISMB has been able to partner with the PPCTS and help support the upcoming 7th Pan Pacific Connective Tissue Societies Symposium to be held in Cairns, Australia, from October 28 to November 1, 2007. This symposium will now officially be the 7$^{th}$ Pan Pacific Connective Tissue Societies Symposium in association with ISMB. With the aims of stimulating the participation of young people in matrix biology research regionally (Pan-Pacific) and, recognizing a significant advance in matrix biology research internationally, we are able to announce several awards.

**The ISMB-*Matrix Biology* Best Poster Awards at the 7$^{th}$ PPCTS/ISMB-Symposium**:

1. US$500 award for the best poster of a student.
2. US$500 award for the best poster of a postdoctoral fellow (within 5 years of graduation from Medical, Dental or Graduate School).

**The ISMB-*Matrix Biology* Best Paper Award**
This is an US$1000 award to the authors of a recent outstanding paper from an ISMB member, published in *Matrix Biology* within the period July 1$^{st}$ 2006 – June 30$^{th}$ 2007. The winning paper, which will be announced at the PPCTS/ISMB meeting, would be an Editors' Choice paper, selected by a majority of Editorial Board members. If you are wondering what happens if you are not an ISMB member or are a lapsed ISMB member? Don't worry, ISMB membership can easily be fulfilled either by the recipient joining the ISMB or by renewing his/her membership by paying up! (In that regard, Peter tells us that we have many ISMB members in the lapsed category). Can we expect a rush to join the ISMB or renew membership? I hope so!

For these awards, the abstracts, with 3 figures and references, of the winners will be published in *Matrix Biology* after the symposium, with a photograph of the first author/presenting student/postdoc and an announcement of the Awards received.

**ISMB lecture at 7$^{th}$ PPCTS/ISMB Symposium**
With the financial prudence of our Treasurer, you will be happy to know that we can draw from ISMB resources and sponsor one of the talks at the 7$^{th}$ PPCTS/ISMB

meeting. We hope this talk will be from an up and coming investigator.

**Expanding leadership in the ISMB**
To further strengthen the leadership in the ISMB Council, we have noted that there is a gap in representation from two locations where there are significant research activity in matrix biology – UK and Japan. Therefore we have sought nominations for election of 2 additional members to Council. We are fortunate that we have an outstanding list of leading matrix biologists who have agreed to stand for election. They are **Paul Bishop, George Bou-Gharios, Bruce Caterson, David Hulmes, Kazuhiro Nagata and Yasunori Okada** (see below). Please vote!!!

**Coming up - ISMB Distinguished Investigator Prize**
We plan to launch a new award – the ISMB Distinguished Investigator Prize - to recognize excellence in matrix biology in 2005-2006. There will be no age limit for eligibility for this award. More details next time- watch this space!

Finally I do have a special plea for all ISMB members. We are making a start towards realizing our vision, just think of how much more we could achieve if all lapsed members renewed their membership dues and all helped to recruit new members! Until the next newsletter, all good wishes for success in your research.

Kathy Cheah
President, ISMB

## Notice from the Treasurer

Dear ISMB member,

Did you run into difficulties when trying to access your personal on-line subscription to Matrix Biology? It happened to myself, too. Elsevier has changed the website which entitles you to download papers from the journal. The procedure you should follow from now on is the following:

Go to http://www.sciencedirect.com/matbio. Enter your user name and your password. Now, it should work! It did so for me, at least.

Enjoy reading our society journal.

Peter Bruckner
Secretary / Treasurer

## Election of new ISMB Council members

The ISMB council has decided expand to include more members from two locations with significant research activity in matrix biology that is not currently represented on the Council – UK and Japan. We are fortunate that we have an outstanding list of leading matrix biologists who have agreed to stand for election. They are Paul Bishop, George Bou-Gharios, Bruce Caterson, David Hulmes for the UK position, and Kazuhiro Nagata and Yasunori Okada for the Japanese position.
How to vote:

1) Select your preferred candidate for election to ISMB Council from the list below– One Japanese and one British researcher

2) Email the names of your two preferred candidates in the body of an email to: peter.bruckner@uni-muenster.de using the subject header 'ISMB Election'.

**UK candidates**
Paul Bishop
George Bou-Gharios
David Hulmes
Bruce Caterson

**Japanese candidates**
Kazuhiro Nagata
Yasunori Okada

Brief biographical sketches of each candidate (in no particular order!) are below. Voting closes Friday May 25th.

**Paul Bishop**
I am currently Professor of Ophthalmology and Matrix Biology at the University of Manchester. I am a practising clinician and am a Consultant Ophthalmologist at Manchester Royal Eye Hospital, specialising in the treatment of medical retinal disease. I whilst training as an ophthalmologist I completed a PhD (in 1993) under the guidance of Dr. Shirley Ayad studying vitreous collagens. From 1991-2006, I held the consecutive Wellcome Trust Clinical Research Fellowships, culminating in a Senior Clinical Fellowship; this allowed me to establish an independent research group. I have been a member of the Wellcome Trust Centre for Cell-Matrix Research at the University of Manchester since its inception in 1995 and my research laboratory is located in this Centre. My research interests include matrix biology of the eye, the structure and functions of members of the small leucine-rich repeat proteoglycan family (especially opticin and decorin), and most recently the regulation of angiogenesis by extracellular matrix.

**George Bou-Gharios**
I am currently a Senior lecturer in the Department of Renal Medicine in the Faculty of Medicine, Imperial College London (Hammersmith Hospital Campus).

For many years I have been involved in collagen type I transcriptional regulation using transgenic analysis to determine non-coding sequences that target cell-specific lineages. After a PhD from University of London and a brief spell in Dame professor Black's lab, I spent two

years in the laboratory of Benoit de Crombrugghe at the University of Texas working on the regulation of the mouse pro alpha 2 (I) collagen gene. Following this I returned to Imperial College London to investigate collagen type I regulation and fibrosis in dystrophic muscles. My current focus is to investigate:

*The molecular and cellular events leading to fibrosis in connective tissue diseases* - We are using the transgenic approach we have developed to target the processes and cells that are involved in the progressive, degenerative diseases affecting connective tissues (fibrosis) which currently pose insurmountable problems in terms of clinical management.

*Regulatory factors in fibroblast lineages* – Although mesenchymal progenitor cells, such as myoblasts, chondrocytes, osteoblasts and lipocytes, specific sets of critical transcription factors have been identified, the transcriptional mechanisms that result in fibroblast characteristics have not yet been elucidated. Our approach is to use embryonic fibroblasts, which are characterised by high levels of expression of type I collagen. We have clearly established that specific cis-acting regions direct expression of *COL1A2* in different fibroblast-specific, which we are targeting to establish the presence of key transcription factors that determine this "default" fibroblastic state.
For more information visit:
http://www1.imperial.ac.uk/medicine/people/g.gharios/

**David Hulmes**
Current position: Director of Research, Institute of the Biology and Chemistry of Proteins, Lyon, France.

1972-1975: PhD, University of Oxford (D.Phil., molecular biophysics)
1976-1978: EMBO/EMBL Fellow, European Molecular Biology Organisation, Grenoble Outstation, France.
1978-1981: Research Fellow in Medicine, then Assistant Professor in Biochemistry, Developmental Biology Laboratory, Massachusetts General Hospital, Harvard Medical School, Boston, Mass, USA.
1981-1985: Research Fellow, then MRC Senior Research Fellow, Department of Medical Biophysics, University of Manchester.
1985-1995: Lecturer, Senior lecturer, then Reader in Biochemistry, University of Edinburgh

Current research is focussed on the structure and function of tolloid proteinases and associated regulatory proteins. We aim to elucidate the molecular mechansims of these proteins as well as their role in animal models of tissue remodelling, with a view to designing novel therapies for tissue repair. Another area of interest is the construction of three-dimensional scaffolds for applications in tissue engineering of the cornea.

**Bruce Caterson**
Bruce Caterson is currently the Chairman of the British Society for Matrix Biology (BSMB) and President of the British Orthopaedic Research Society (BORS) and in the past has been President of the Society for Back Research (UK) and President of the Orthopaedic Research Society (ORS) in the USA. He has degrees from Monash University, Clayton, Victoria, Australia, (B.Sc. and Ph.D. in Biochemistry, 1971 & 1976, respectively). From 1975-1995 he spent 20 years in academia in the USA: 1975-82 West Virginia University; 1989-95, Professor & Endowed Chair in Orthopaedic Research, University of North Carolina at Chapel Hill, NC. In 1995 he moved to Cardiff University, Wales, UK as a Professor of Biochemistry in the Connective Tissue Biology Group within the School of Biosciences and Associate Director of Musculoskeletal Research in the School of Medicine.

His primary research interests have centred around using monoclonal antibody technologies to study matrix proteoglycan structure, function and metabolism in health and disease with particular emphasis on musculoskeletal tissues. In the past 30 years he has published a total of 136 full papers and 26 chapters and reviews. In 1986 he was awarded the Benedum Distinguished Scholar Award in Biosciences and Medicine from West Virginia University and in 1998 the Kappa Delta Elizabeth Winston Lanier Award for Outstanding Orthopaedic Research from the American Academy of Orthopaedic Surgeons and Orthopaedic Research Society.

**Kazuhiro Nagata**
Current position: Professor and Chairman, Department of Molecular and Cellular Biology, Institute for Frontier Medical Sciences, Kyoto University

1979: Ph. D. Kyoto University (Biophysics)
1971 – 1976: Research Fellow, Central Research Institute, Morinaga Milk Industry, Ltd.
1976 – 1979: Research Fellow, Chest Disease Research Institute, Kyoto University
1979 – 1986: Lecturer, Chest Disease Research Institute, Kyoto University
1984 – 1986: Visiting Associate, Laboratory of Molecular Biology, National Cancer Institute, NIH
1986 – 1998: Professor and Chairman, Department of Cell Biology, Chest Disease Research Institute, Kyoto University

Current research is focused on the essential role of Hsp47, which is a collagen-specific molecular chaperone,in the biosynthesis and folding of collagens in the ER. We are also interested in exploring the therapeutic strategy for fibrotic diseases including liver cirrhosis by developing the agents which inhibit Hsp47 functions. More generally, on-going projects in our group are focused on quality control systems of nascent and/or misfolded proteins in the ER.

**Yasunori Okada**
Yasunori Okada, M.D., Ph. D.
Current position: Professor and Chairman, Department of Pathology, School of Medicine, Keio University 35 Shinanomachi Shinjuku-ku, Tokyo 160-0016, Japan

1974: M.D., School of Medicine, Kanazawa University
1978: Ph.D., Division of Research in Medicine, Graduate School, Kanazawa University
1984-1986: Fogarty International Research Fellow (NIH), UMDNJ-Rutgers Medical School, New Jersey, U.S.A. Professor E. D. Harris, Jr. (Supervisor),
1994-1997: Professor, Department of Molecular Immunology and Pathology, Cancer Research Institute, Kanazawa University
1997-2001, Professor, Department of Pathology, School of Medicine, Keio University

Our research group has focused on the studies of the MMP (matrix metalloproteinase) and ADAM (a disintegrin and metalloproteinase) gene families. We are trying to elucidate the molecular mechanisms of the tissue destruction and remodeling through excessive metabolism of tissue microenvironmental factors such as extracellular matrix, cytokines/growth factors and membrane proteins by MMPs and ADAMs. The major pathological conditions we are interested in include rheumatoid arthritis, osteoarthritis, and cancer proliferation and progression.

## Meeting Announcements

***FEBS Advanced Lecture Course***
"Matrix Pathobiology, Signaling and Molecular Targets, FEBS-MPST 2007"
Patras, Greece
May 21-26, 2007
www.chemistry.upatras.gr/febs-mpst2007

***13th Annual Canadian Connective Tissue Conference***
Toronto, Canada
May 24-26, 2007
www.utoronto.ca/cctc2007
E-mail: cctc2007@utoronto.ca
Organised by Wolfgang Vogel, Cari Whyne and Burton Yang

***Gordon Research Conference "Cell Contact & Adhesion"***
Il Ciocco Barga, Italy
May 27 - June 1, 2007
Chair: Elisabetta Dejana
Vice Chair: Pierre McCrea
www.grc.org/programs.aspx?year=2007&program=cellcont

***Gordon Research Conference "Matrix Metalloproteinases"***
Il Ciocco Barga, Italy
June 3-8, 2007
Chair: Carlos Lopez-Otin
Vice Chair: Carl P. Blobel
www.grc.org/programs.aspx?year=2007&program=matrmet

***Gordon Research Conference "Tissue Repair & Regeneration"***
Colby-Sawyer College, New London, NH, USA
June 17-22, 2007
Chair: Jack Gauldie
Vice Chair: Luisa A. Dipietro
www.grc.org/programs.aspx?year=2007&program=tissue

***Gordon Research Conference "Bones & Teeth"***
University of New England, Biddeford, ME, USA
July 15-20, 2007
Chair: Pamela G. Robey
Vice Chair: Brendan F. Boyce
www.grc.org/programs.aspx?year=2007&program=bones

***Stem Cell Manchester meeting***
University of Manchester, UK
July 16-18, 2007
Organised by Tim Hardingham
Contact Sarah Farrar (sarah.farrar@manchester.ac.uk)

***Gordon Research Conference "Collagen"***
Colby Sawyer College, New London, NH, USA
July 22-27, 2007
Chair: David E. Birk
Vice Chair: Leena Bruckner-Tuderman
www.grc.org/programs.aspx?year=2007&program=collagen

***Gordon Research Conference "Biomaterials: Biocompatibility / Tissue Engineering"***
Holderness School, Plymouth, NH, USA
July 22-27, 2007
Chair: Andres J. Garcia
Vice Chair: William M. Reichert
www.grc.org/programs.aspx?year=2007&program=biomat

***Gordon Research Conference "Elastin and Elastic Fibers"***
University of New England, Biddeford, ME, USA
July 29 - August 3, 2007
Chair: Elaine C. Davis
Vice Chair: Anthony S. Weiss
www.grc.org/programs.aspx?year=2007&program=elastin

***Gordon Research Conference "Small Integrin-Binding Proteins"***
University of New England, Biddeford, ME, USA
August 5-10, 2007
Chairs: Neal S. Fedarko & Cecilia M. Giachelli
Vice Chairs: Susan R. Rittling & Marc D. McKee
www.grc.org/programs.aspx?year=2007&program=smallint

***5th International Conference on Proteoglycans***
Rio de Janeiro, Brazil
September 16-20, 2007
www.bioqmed.ufrj.br/pgrio2007/

***XIII$^{th}$ International Symposium on Basement Membranes and Collagen IV Symposium***
in Honor of Klaus Kühn
Center for Biochemistry, Medical Faculty, University of Cologne, Germany
September 19-22, 2007
Email: bm-2007@uni-koeln.de
www.BM2007.uni-koeln.de

***5th General Meeting of the International Proteolysis Society***
Patras, Greece
20-24 October 2007,
Chair: Georgia Sotiropoulou, Patras (Greece)
ips2007@upatras.gr
Vice Chairs: Francesc X. Aviles, Barcelona (Spain) and Matthew Bogyo, Stanford (USA)
Abstract Deadline: July 10, 2007, and June 10, 2007 (for oral presentations)
http://www.ips2007patras.gr/

***7th Pan Pacific Connective Tissue Societies Symposium***
Shangri-La Resort, Cairns, Australia
October 28 – November 1, 2007
Conference convener: Shireen Lamande
E-mail: connective@asnevents.net.au
www.connectivetissue2007.org/

***World Congress on Osteoarthritis***
Miami Beach, Florida, USA
December 6-9, 2007

***XXI meeting of the Federation of European Connective Tissue Societies***
Marseille, France
July 9-13, 2008
Chair: Phillippe Charpiot
philippe.charpiot@pharmacie.univ-mrs.fr
Vice-chair: Sylvie Ricard-Blum
s.ricard-blum@ibcp.fr

***The 16th Biennial National Conference on Osteogenesis Imperfecta***
Crystal City, VA, USA
August 1-3, 2008
www.oif.org/site/PageServer?pagename=06conf_splash&JServSessionIdr006=ccdbf0x1f2.app1a

***American Society for Matrix Biology 2008 meeting***
San Diego, CA, USA
December 7-11, 2008
Chair: Bill Parks

Detail information on registration and call for abstracts will be announced in the next ASMB newsletter and on the ASMB website at www.asmb.net.

## Matrix Research Update

Articular cartilage and growth plate defects are associated with chondrocyte cytoskeletal abnormalities in Tg737$^{orpk}$ mice lacking the primary cilia protein polaris

McGlashan SR[1], Haycraft CJ[2], Jensen CG[1], Yoder BK[2], Poole CA[3]

1) Department of Anatomy with Radiology, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand
2) Department of Cell Biology, University of Alabama at Birmingham, Birmingham, Alabama, USA
3) Section of Orthopaedic Surgery, Department of Medical and Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

Primary cilia are highly conserved organelles found on almost all eukaryotic cells. Tg737$^{orpk}$ (*orpk*) mice carry a hypomorphic mutation in the *Tg737* gene resulting in the loss of polaris, a protein essential for ciliogenesis. *Orpk* mice have an array of skeletal patterning defects and show stunted growth after birth, suggesting defects in appositional and endochondral development. This study investigated the association between *orpk* tibial long bone growth and chondrocyte primary cilia expression using histomorphometric and immunohistochemical analysis. Wild type chondrocytes throughout the developing epiphysis and growth plate expressed primary cilia, which showed a specific orientation opposite to the articular surface in the first 7-10 cell layers. In *orpk* mice, primary cilia were identified on very few cells and were significantly shorter. *Orpk* chondrocytes also showed significant increases in cytoplasmic tubulin, a likely result of failed ciliary assembly. The growth plates of *orpk* mice were significantly smaller in length and width, with marked changes in cellular organization in the presumptive articular cartilage, proliferative and hypertrophic zones. Cell density at the articular surface and in the hypertrophic zone was significantly altered, suggesting defects in both appositional and endochondral growth. In addition, *orpk* hypertrophic chondrocytes showed re-organization of the F-actin network into stress fibres and failed to fully undergo hypertrophy, while there was a marked reduction in type X collagen sequestration. These data suggest failure to form a functional primary cilium affects chondrocyte differentiation via the primary cilium and the associated cytoskeleton and results in delayed chondrocyte hypertrophy within the *orpk* growth plate.

## Job Advertisements – Group Leader

### Junior Group Leader positions

The Ministry of Innovation, Science, Research, and Technology of the German State North-Rhine / Westfalia (NRW) will establish in January 1, 2008 3 Junior Group Leader positions with an interest in stem cell research. All specialties within this field will be considered. Young scientists having a proven record of excellence and independent research experience are encouraged to apply. Applications are not addressed directly to the Ministry but through NRW universities, who will be responsible for 30 % of the costs of successful projects. Procedural details are available on http://www.stammzellen.nrw.de/grafik/Call_JuniorgroupsNRW.pdf and http://www.stammzellen.nrw.de/en/startseite.html.

The University of Muenster is supporting this programme. If you are interested in filing an application, please, send a brief sketch of your research proposal stating your specific interest, a short CV, and publication list (2000-2007) to Dr. Sigrid Nikol, University Hospital of Muenster, Department of Internal Medicine C, Albert-Schweitzer-Str. 33, 48149 Münster, E-mail: nikol@uni-muenster.de not later than May 15. Thereafter, you may be requested to write a full application. Full applications are due July 1 and should follow the guidelines of the programme: http://www.stammzellen.nrw.de/grafik/Guidelines_JuniorgroupsNRW.pdf.

## Job Advertisements – Post-doctoral

### Post-doctoral Position

Various projects are available in the lab to study structural and functional aspects of extracellular matrix components involved in genetic disorders of the cardiovascular and skeletal system. The projects focus on components of the microfibril/elastic fiber system. A broad spectrum of methods will be involved including recombinant protein production, cell culture, protein chemistry, immunological methods, proteomics approaches and gene targeting experiments in mice. For further information, please see lab website. Applicants are expected to hold a PhD in an area related to extracellular matrix biology and to have an excellent academic record. Expertise in protein chemistry, mass spectrometry, recombinant protein expression or animal handling is highly advantageous. Candidates should send by email a cover letter, a complete curriculum vitae and the names of two references to:

Dr. Dieter Reinhardt
McGill University
Department of Anatomy and Cell Biology
3640 University Street
Montreal, Quebec H3A 2B2, Canada
Phone: +1 (514) 398-4243
Fax: +1 (514) 398-5047
E-mail: dieter.reinhardt@mcgill.ca
Web: www.medicine.mcgill.ca/anatomy/reinhardt/

### Post-doctoral fellowships

#### Developmental Biology and Biochemistry of Metalloproteases

Post-doctoral fellowships will be available in 2007 and 2008 to study the biology and biochemistry of ADAMTS proteases. ADAMTS proteases have been implicated in arthritis, inherited connective tissue disorders, cell migration and angiogenesis. The overall goal of the laboratory is to understand the role of ADAMTS proteases in molecular networks.

The laboratory has characterized a number of ADAMTS proteases and ADAMTS-like molecules. Ongoing projects include the mechanisms of phenotypes in ADAMTS null mice, analysis of post-translational modification of ADAMTS proteases and ADAMTS-like molecules, proteomics for identification of substrates and intermolecular interactions, and understanding the role of ADAMTS in vascular biology and cancer.

The laboratory will suit highly motivated new or recent PhD or MD/PhD graduates who are interested in augmenting or developing skills in mouse genetics, embryology, cell biology, enzymology and protein chemistry. The laboratory offers a stimulating and constructive environment for your professional development. The Lerner Research Institute has state of the art research facilities in a major clinical center, the Cleveland Clinic Foundation. Cleveland and its vicinity offer an affordable, high quality of life with outstanding recreational and cultural opportunities. Most recent publications

Koo, B-H, Longpre, J-M, Somerville, RPT, Alexander, JP, Leduc, R., Apte, SS. Regulation of ADAMTS9 secretion and enzymatic activity by its propeptide. J Biol Chem. 2007 April 3; [Epub ahead of print]

Wang LW, Dlugosz M, Somerville RP, Raed M, Haltiwanger RS, Apte SS. O-Fucosylation of thrombospondin type 1 repeats in ADAMTS like-1/punctin-1 regulates secretion: Implications for the ADAMTS superfamily. J Biol Chem. 2007 Mar 29; [Epub ahead of print]

Koo, B-H, Longpre, J-M., Somerville, RPT, Alexander, J.P., Leduc, R.,Apte, SS. Cell surface processing of pro-ADAMTS9 by furin. *J Biol Chem, 2006* 281(18):12485-94

LeGoff C, Somerville, RPT, Kesteloot, F, Powell, K, Birk, D.E., Colige, A., Apte, S.S. Regulation of procollagen amino-propeptide processing during mouse embryogenesis by specialization of homologous ADAMTS proteases; Insights on collagen biosynthesis and dermatosparaxis. *Development, 2006* 133(8):1587-96

**Contact: Suneel S. APTE, MD, PhD (aptes@ccf.org)**

## Postdoctoral positions

**Developmental Genomics & Skeletal Research**

**Department of Biochemistry, University of Hong Kong, Hong Kong**

Applications are invited for two postdoctoral fellowships under a Hong University Grants Council's Area of Excellence (AoE) research programme entitled *Developmental Genomics & Skeletal Research.* This programme focuses on key issues at the frontier of developmental biology and skeletal research related to the formation and growth of cartilage and bone and the maintenance of skeletal function. Part of the programme aims to understand the molecular genetic and developmental controls regulating cartilage formation and maturation in skeletal growth especially the molecular controls of terminal differentiation and cell death in chondrocytes; the role of the ECM, its interactions and turnover. Another part of the programme aims to identify genetic risk factors and understand molecular mechanisms underlying skeletal disorders – both developmental and degenerative. The impact of stress responses on skeletal growth and degenerative intervertebral disc disease are areas of focus.

Interested candidates should send their curriculum vitae to the AoE Director, Prof. K.S.E. Cheah at biochem@hkusua.hku.hk who may also be contacted for further information on projects.
Closing date: June 15th 2007

Available online at www.sciencedirect.com
ScienceDirect
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MATRIX BIOLOGY
www.elsevier.com/locate/matbio

From the Editor's Desk

# A therapy for myopathy caused by collagen VI mutations?

*Dear readers of Matrix Biology,*

In a previous editorial (Olsen, 2003) I discussed the intriguing studies of Irwin et al. (2003) on the pathogenetic mechanisms underlying an early-onset myopathic syndrome seen in *Col6a1* null mice. The syndrome resembles autosomal dominant Bethlem myopathy in humans (Bonaldo et al., 1998), caused by mutations in one of the three collagen VI genes. Irwin et al. (2003) demonstrated that lack of collagen VI in mice results in increased apoptosis of skeletal muscle cells and ultrastructural defects in their mitochondria and the sarcoplasmic reticulum. These defects were traced back to sensitization of the mitochondrial permeability transition pore, known to play a role in apoptosis. When collagen VI-deficient muscles were incubated with the mitochondrial ATP synthase inhibitor oligomycin, the results were mitochondrial depolarization, $Ca^{++}$ deregulation and enhanced apoptosis. In contrast, treatment of the *Col6a1* null mice with Cyclosporin A, known to desensitize the permeability transition pore, resulted in a dramatic recovery from the muscle lesions. This suggested that treating the mitochondrial defect could lead to an amelioration of the muscle phenotype in mice and perhaps even human patients with collagen VI mutations.

These exciting studies have now been taken one important step further towards the clinical goal of developing a therapy for collagen VI-based myopathies in humans. In a recent paper (Angelin et al., 2007), the groups of Bonaldo and Bernardi report on studies of five patients with Ullrich congenital muscular dystrophy, a severe muscle wasting disease in which muscle tissue contains no or severely reduced levels of collagen VI. In quadriceps muscle biopsies, the frequency of apoptotic nuclei was significantly increased compared to muscle from a healthy donor. When isolated muscle cells were grown *in vitro*, patient cells showed higher levels of apoptosis than control cultures. Remarkably, addition of collagen VI to cultures of mutant cells or treatment with Cyclosporin A brought levels of apoptosis down to control levels.

Addition of oligomycin to muscle cell cultures did not cause mitochondrial depolarization in normal cells, but resulted in depolarization in all patient cell samples, including one sample for which identification of a collagen VI mutation was lacking although the sample came from a patient with the clinical and immunohistochemical signs of Ullrich congenital muscular dystrophy. Therefore, the authors suggest that the abnormal mitochondrial oligomycin response may be a useful diagnostic tool for patients with collagen VI-associated disorders even in cases where the mutations have not been identified. Following treatment with Cyclosporin A, addition of collagen VI, or addition of a $Ca^{++}$-chelator, the mitochondrial depolarization response to oligomycin was normalized in the patient cultures. Furthermore, electron microscopy demonstrated alterations in size and structure of mitochondria in mutant cells; plating on collagen VI or treatment with Cyclosporin A normalized the mitochondrial ultrastructure. Finally, by using a Cyclosporin A variant that affects the mitochondrial transition pore without affecting calcineurin, another target of Cyclosporin A, Angelin et al. (2007) show that the effects of Cyclosporin A on the mutant cells are not caused by effects mediated by calcineurin.

These are indeed studies of significant clinical promise. Recently, analyses of mice with mutations in the extracellular matrix component fibrillin have led to the discovery that treatment of a downstream consequence (activation of TGFβ1) may provide a cure for the lung and cardiovascular complications of Marfan syndrome (Habashi et al., 2006; Olsen, 2006). Clinical trials of Losartan to block TGFβ1 activity in patients with Marfan syndrome are underway. The promising studies of Angelin et al. (2007) suggest that a small trial to benefit patients with Bethlem myopathy and Ullrich congenital muscular dystrophy may not be too far behind.

## References

Angelin, A., Tiepolo, T., Sabatelli, P., Grumati, P., Bergamin, N., Golfieri, C., Mattioli, E., Gualandi, F., Ferlini, A., Merlini, L., et al., 2007. Mitochondrial dysfunction in the pathogenesis of Ullrich congenital muscular dystrophy and prospective therapy with cyclosporins. Proc. Natl. Acad. Sci. U. S. A. 104, 991–996.

Bonaldo, P., Braghetta, P., Zanetti, M., Piccolo, S., Volpin, D., Bressan, G.M., 1998. Collagen VI deficiency induces early onset myopathy in the mouse: an animal model for Bethlem myopathy. Hum. Mol. Genet. 7, 2135–2140.

Habashi, J.P., Judge, D.P., Holm, T.M., Cohn, R.D., Loeys, B.L., Cooper, T.K., Myers, L., Klein, E.C., Liu, G., Calvi, C., et al., 2006. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science 312, 117–121.

Irwin, W.A., Bergamin, N., Sabatelli, P., Reggiani, C., Megighian, A., Merlini, L., Braghetta, P., Columbaro, M., Volpin, D., Bressan, G.M., et al., 2003. Mitochondrial dysfunction and apoptosis in myopathic mice with collagen VI deficiency. Nat. Genet. 35, 367–371.

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Olsen, B.R., 2006. From the Editor's desk. Matrix Biol. 25, 269–270.

0945-053X/$ - see front matter 
doi:10.1016/j.matbio.2007.07.004

# 7th Pan Pacific Connective Tissue Societies Symposium

## 28th October - 1st November 2007
## Shangri-La Resort, Cairns, Australia

## Abstract Submission & Registration Are Open!

**Registrations & Abstracts can ONLY be submitted online.**
**Accommodation can also be booked online through the registration process.**

**17th August 2007 - Early Bird Registration Deadline**

**New Investigator & Student Poster Awards will be granted.**
**Please select this option when submitting you abstract if you wish to be considered.**

## Please visit www.connectivetissue2007.org for all details

**Confirmed Invited Speakers**
Reinhard Fassler (Germany)
David Eyre (USA)
Kaz Nagata (Japan)
Chris Overall (Canada)
Yoshi Ninomiya (Japan)
Kevin Campbell (USA)
Eri Arikawa-Hirasawa (Japan)
Renato Iozzo (USA)
Kishore Prayaga (AU)
Amanda Fosang (AU)
Kathy Cheah (HK)
Bruce Caterson (UK)
Stan Gronthos (Australia)

**Conference Convenor**
Dr Shireen Lamande
shireen.lamande@mcri.edu.au

**Conference Secretariat**
ASN Events Pty Ltd
Ph: 03 5983 2400
Email: mp@asnevents.net.au

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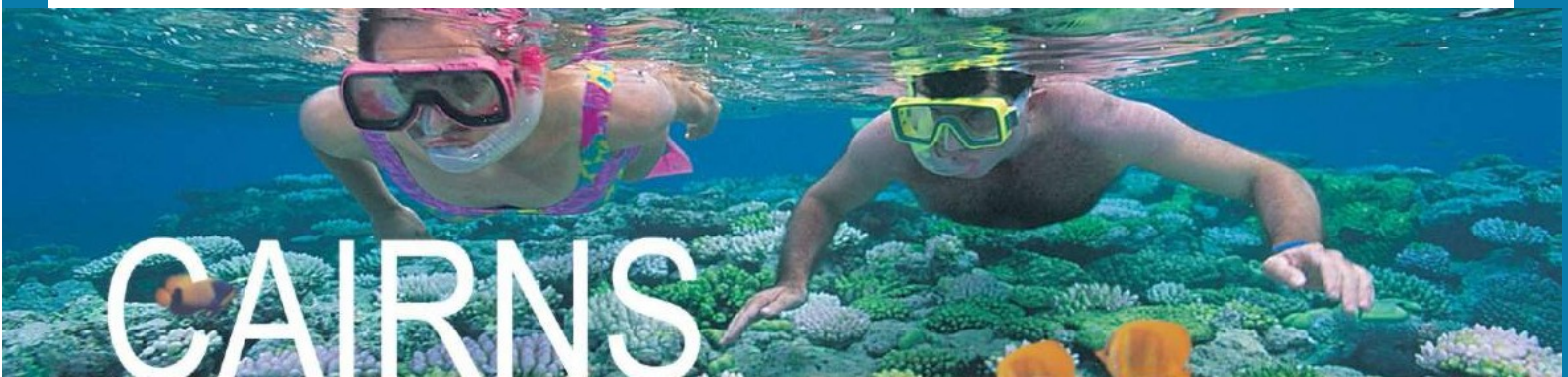

# SAVE THE DATES!  ASMB 2008 Meeting

To be held at the Manchester Grand Hyatt in San Diego, California
Program Chair: Bill Parks, University of Washington - Seattle
Co-Chairs: Jaime Fitzgerald, Oregon Health Science University - Portland, Karen Lyons, University of California – Los Angeles, Joanne Murphy-Ullrich, University of Alabama – Birmingham, Ambra Pozzi, Vanderbilt University, Ralph Sanderson, University of Alabama – Birmingham, Marian Young, National Institute of Dental and Craniofacial Research and Peter Yurchenco, UMDNJ Robert Wood Johnson Medical School.

Detail information on registration and call for abstracts will be announced in the next ASMB newsletter and on the ASMB website at www.asmb.net.