International Society for Matrix Biology Newsletter

No. 5 - December 2006

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From the President's Desk

ISMB - Looking Forward: Fostering, Connecting and Networking Matrix Biologists World-Wide

When I took up the Presidency a few months ago I remarked in the August issue of the ISMB Newsletter that since ISMB was established some time ago, we have seen changes in the field and in the international community of matrix biologists. Awareness of the important role of the matrix in biological processes has become increasingly apparent. Nowadays publications on the functional and biological roles of the ECM appear in a wide range of journals serving different disciplines – clinical sciences, cell, molecular and developmental biology, cancer biology, biotechnology, neurobiology and so on. Societies for these fields often spring up to serve the scientific community. Often these societies' major role is in organizing regular conferences. In matrix biology there are several strong and active national societies in different regions – such as in Europe, North America, Japan and Australia.

I wrote then of my strong view that ISMB can have an important role to play internationally and that there is a need to develop a new vision/role for ISMB that will increase its relevance to the international matrix biology community. Since then the Council has been actively debating the future role of ISMB and how the society can help live up to its aims. We all agree that ISMB should be a truly international society and should have a **distinct** role apart from the national societies. But *distinct* does not mean separation. Matrix biologists are distributed in roughly three main geographical areas – in North America, Europe and Asia Pacific. We feel that ISMB can support and facilitate connections between the national societies world-wide. So the mission of Council for ISMB in the coming years is to facilitate interactions and collaborations across continents and foster the development of the careers of matrix biologists. By expanding the ISMB network and connecting matrix biologists across the world we can truly become the international voice of the matrix biology community.

How will we do that? As a start we hope that many more matrix biologists will join the society and contribute towards achieving the society's vision. In 2006 the ISMB contributed to the FECTS meeting held in Oulu, Finland and will also contribute to the ASMB annual meeting in 2008. In 2007 ISMB will contribute to the Pan-Pacific Connective Tissue Societies symposium in Australia. We hope we can arrange reduced registration rates at these upcoming meetings.

ISMB supports the career development of young matrix biologists by recognizing excellence through the Rupert Timpl prize and lecture at the FECTS meetings, and by awarding travel grants to attend the FECTS and ASMB meetings. In 2007 we plan to introduce 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.

In the future with increased membership numbers and willing sponsors, we can also envisage more awards and short term training fellowships of 2-3 months for young scientists to visit laboratories in a different continent to their own. Such "visitorships" should help build bridges between research groups. We can run courses on specialized techniques or advanced study institutes on key issues in the field. These are just some ideas to start with.

So what will be the immediate benefits of ISMB membership?

- Postdoctoral fellows and postgraduate members will be eligible for the travel awards to the FECTS and ASMB meetings.
- Members can contribute towards identifying and recognizing research excellence in matrix biology by nominating:
  - Junior matrix biologists for the Rupert Timpl Prize.
  - Matrix biologists for the new ISMB Distinguished Investigator Award.
- Members will qualify for reduced rate electronic subscription to *Matrix Biology*, the official journal of the society.
- Members will automatically receive the ISMB Newsletter, and through the newsletter, reach the matrix biology community at large i.e. members can become more connected to matrix biologists world-wide.
- The more members we have the wider the range of benefits – do remember to renew your membership, and if you are not a member, do join us and strengthen the international community of matrix biologists, help promote the field and
- Of course volunteers to help with activities and ideas as well as sponsorship are especially welcome.

Resources for the prizes and travel bursaries will come from the membership dues and donations, so If you are an ISMB member, please help recruit new members. If you are not a member, we hope that you will be persuaded to join us. And of course most important, regardless of whether you are a member or not, letting us know your views and ideas. The Council and I look forward to hearing from you. All the very best to all of you for 2007.

Kathy Cheah, President, ISMB

From the Treasurer's Desk

This is the time to renew your ISMB-membership and the Council has introduced several changes. You now will have four possible ways to become an ISMB member or to renew your membership:

1) You are a regular member and no longer wish to subscribe to Matrix Biology, the official journal of our society. This would be the preferred membership if you have access to Matrix Biology by an institutional subscription. However, you will keep supporting the activities of our society. The scope of these ISMB-activities has increased to include not only the "Rupert Timpl Award" (issued biannually at FECTS-meetings), but also the "Distinguished Matrix Biologists Award" (issued biannually at ASMB-meetings), as well as Travel Fellowships to ASMB-, FECTS-, or the Pan Pacific Connective Tissue Meetings. Also, the organisers of the large meetings (FECTS, ASMB, PPCTSS) will be encouraged to reduce the registration fees for ISMB-members.

Of course, there is a down-side to this. The Council saw no option but to agree to a modest increase of the membership fee from currently EUR 30 to EUR 50 for regular members. This may allow us to keep the above mentioned activities going and even to envisage new things, such as introducing matrix biology as a scientific field to countries where currently no national societies are in existence. Or to start courses or internal publications in methods in matrix biology. Your membership fee is: EUR 50 (ca. USD 66).

Elsevier offers much reduced, personal subscriptions to Matrix Biology to ISMB-members. They have only marginally increased their rates over those of last year. We recommend that you take advantage of this offer if you have no institutional access to our journal. Therefore:

2) You are a regular member and you want to keep Matrix Biology in print and by online access through ScienceDirect. Your membership then is: EUR 150 (ca USD 196).

3) You are a regular member and you want to keep online access to Matrix Biology. Your membership then is: EUR 95 (ca USD 124).

4) You are a student or a young post-doc. Your membership fee does not change but your benefits have increased. You pay: EUR 20 (ca USD 26).

We would be very grateful if you settled your account swiftly as some of you have done in the past. Let us help to keep the society going.

You can join the ISMB or renew your membership online (www.ismb.org) or by the form found at the end of this Newsletter. Please, complete this form and send it by FAX or e-mail to our secretary / treasurer, Peter Bruckner

(FAX: +49 251 835 5596, peter.bruckner@uni-muenster.de).

Seasons Greetings to all of you!

Peter Bruckner, Treasurer, ISMB

International Matrix Biology News

British Society for Matrix Biology (BSMB)

The BSMB has over 400 members many of whom actively participate in the two meetings that take place each year. In April 2006 there was a meeting at Cambridge University organized by Dr. Graham Riley and Professor Gill Murphy with the catchy title "Proteases: the cutting edge of cell biology". Our second meeting of the year, in September was run by Dr Drew Rowan at Newcastle University with the title "The multi-dimensional matrix".

The BSMB is run by an active committee that has recently decided to institute two awards for excellence in matrix biology research. The BSMB Fell-Muir award will recognize members who have contributed to both the society and the field of matrix biology over a number of years. The first recipient will be Professor Michael Grant (Manchester University) who will present a lecture at the Spring meeting in Sheffield in 2007. The annual young investigator award will be presented at our September meeting and will recognize excellent scientific contributions by our younger members.

Members of BSMB are not only based in the United Kingdom. Some live elsewhere in Europe or on other continents. We would be delighted to receive membership applications from any matrix biologist anywhere in the world. Furthermore, if you know that you will be in the UK at the time of one of our meetings we would be happy to try and facilitate your scientific participation. Please contact the Chairman or Honorary Secretary well ahead of the meeting date.

For further information about The BSMB, please visit our website: http://www.bsmb.ac.uk/

Bruce Caterson (Chairman)
Anthony Hollander (Honorary Secretary)

American Society For Matrix Biology

ASMB held a fantastic national meeting in Nashville, TN this past November. Our keynote speaker Hal Moses, Vanderbilt University, provided the latest news on TGFß and cancer. ASMB presented several awards during the meeting. Bjorn Olsen, Harvard University, received the Senior Investigator Award and David Calderwood, Yale University, received the Junior Investigator Award. In addition, ASMB provided 15 students and postdoctoral fellows with travel awards. The meeting abstracts, originally published in *Matrix Biology*, and the Keynote Address will be posted to the ASMB web site after the new year. Please visit our updated website for new features http://www.asmb.net.

In addition to a successful meeting, ASMB is proud to announce that we had a record number of members, 450, in 2006. We invite you to join this matrix biology community by visiting our web site http://www.asmb.net (only $90/year or $150 for two years). ISMB members might also be interested in the very active list of available positions other matrix-related information contained on the web site. We look forward to seeing our international matrix friends at our 2008 meeting in San Diego.

Linda J. Sandell, President, ASMB

David Calderwood and Amber Pozzi


Linda Sandell and Billy Hudson

Finnish Society of Connective Tissue Researchers

The Finnish Society of Connective Tissue Researchers had the honor to host the XXth Meeting of the Federation of European Connective Tissue Societies in Oulu, Finland, July 1-5, 2006. The Meeting was a joint meeting with the International Society for Matrix Biology. The Meeting had 429 participants, including 30 invited speakers and workshop chairs. The Keynote speakers were Dr. Darwin J. Prockop, Tulane University Health Sciences Center, New Orleans, USA: "The reparative power of multipotent stromal cells from marrow and other tissues" and Dr. Kari Alitalo, Biomedicum Helsinki, University of Helsinki, Finland : "Lymphangiogenesis in development and human disease". The Meeting programme consisted of 17 plenary lectures, 13 workshops with altogether 89 short talks, and 305 posters. You are welcome to have a look at the Meeting photos at:
http://www.biocenter.oulu.fi/fects_photo_gallery.html.

Swedish and Finnish Societies of Connective Tissue Researchers

The 4th Swedish-Finnish Connective Tissue Meeting will be arranged in Lund, Sweden, April 13-14, 2007. Members of the organizing committee are Professor Dick Heinegård, Professor Anders Malmström and Docent Madeleine Durbeej-Hjalt. For registration, contact . The registration deadline is Januray 29th 2007. Keynote lectures will be given by Dr. Peter D. Yurchenco, Robert Wood Johnson Medical School, Piscataway, USA, and Dr. Bjorn R. Olsen, Harvard School of Dental Medicine, Boston, USA.

Canadian Connective tissue Conference

The inaugural Canadian Connective Tissue Conference, organized by Prof. A.R. Poole, was held in Montreal in June 1995 and has since been a highly successful annual event. The conference brings together over 150 scientists from Canada, the United States and abroad working in the connective tissue research field, and we are pleased to announce that the 13th Annual Canadian Connective Tissue Conference, co-organized by Wolfgang Vogel, Cari Whyne and Burton Yang, will be held in Toronto on May 24 and 25, 2007. The keynote lecture will be given by Bjorn Olsen from Harvard Medical School.

The objective of the CCTC is to provide a forum for exchange and discussion of basic, applied and clinical research in the connective tissue biology. The conference provides a platform for researchers and clinicians alike to present their work, to exchange ideas and to promote connective tissue research in Canada. Featured topics include: matrix receptor signaling, tissue inflammation, biomineralisation, matrix remodeling, mechanobiology, stem cells and tissue engineering.

The senior advisory committee of CCTC2007 include: Jane Aubin (Faculty of Medicine, University of Toronto), Rita Kandel, Marc Grynpas and Kenneth Pritzker (Mount Sinai Hospital) and Jaro Sodek, Chris McCulloch and Morris Manolson (Faculty of Dentistry).

Research trainees and Post-doctoral fellows are especially encouraged to attend and present their work at the CCTC and, as a national Canadian conference, we hope to facilitate their attendance by providing travel awards ($500 each) for trainees attending from outside Quebec and Ontario, in particular from Central Canada, the Maritimes and the West Coast.

Report on the Matrix Biology Society of New Zealand and Australia Conference 2006

This year the MBSANZ conference was a change from our previous style and was held as part of the Australian Health and Medical Research Congress in Melbourne. At first most of us looked shell shocked at the shear size and intensity of the place with trade displays offering us everything from ice cream to massage toys to stuffed wombats, but after a few hours we were strutting around just as confident as the rest of them. One of the advantages of being part of the AHMRC was the amazing plenary speakers that we had the opportunity to listen to. Listening to ground breaking work from Jean Paul Thiery and Rudolf Jaenisch really was a humbling but also inspiring experience.

The MBSANZ conference took place over the first two days of the congress and was jam packed full of amazing speakers. A big thanks must go to everyone who spoke with a special mention to our fantastic international speakers Gillian Murphy, Francesco Ramirez, Tim Hardingham, Ross Garrett and Tony Poole. Most students had their opportunity to shine in the poster sessions and although we were squashed in the back corner of the trade room, our area definitely had a real positive buzz with so much wonderful data for us all to look at and talk about during the tea breaks. It was a hard decision for the judges to make but in the end the winners of the MBSANZ poster prize "Dennis Lowther Award" went to Rishika Pace (first place) and Stephanie Gauci (second place). As winners, both girls were put forward to the AHMRC poster competition and once again they dominated with Rishika Pace awarded the best student poster prize by the National Association of Research Fellows and Stephanie Gauci awarded the "Best of the best student poster award" – a cash prize provided by the Cass Foundation of $5000! A big congratulations to you both.

The conference dinner was definitely a step up and this year we were all treated to an amazing feast of Asian delights at Bok Choy restaurant in Federation Square. The dinner was an excellent way for us all to get together and catch up in a more intimate and relaxed setting as well as celebrate the winners of the Barry Preston award which this year went to a very well deserved Tony Poole and the Young Investigators award which went to Justin Allen.

We must take this opportunity to say a big thank you to Shireen Lamandé for organising such a wonderful program. Hope you enjoyed the champagne! Also on behalf of myself and Mahroo Parsi we would like to say thank you and goodbye to last years student reps Ainslie Roberts and Rena Hirani.

To all students, if you have any questions or queries about the MBSANZ society please feel free to contact us through the website. We also encourage you to tell everyone in the matrix biology field about our wonderful conference and hope to see you all next year. Until next year…….

Charlotte East

Rishika Pace and Stephanie Gaucci

Tony Poole, Shireen Lamandé and Justin Allen

International Society for Matrix Biology

To respond effectively to the needs of the International matrix biology community it is important that countries with a strong matrix biology research presence be represented on the ISMB Council. At the present time the Council has members from Germany, France, Finland, Hong Kong, the US, Canada, and Australia. However, there are currently no members from Japan and the UK who together have 51 ISMB members representing 16% of the total ISMB membership. To address this, the Council is calling for nominations for election to ISMB Council for researchers working in Japan and the UK and other countries not currently represented on the Council. Nominations can be sent to ISMB President, Kathy Cheah (hrmbdkc@hkusua.hku.hk) or ISMB Treasurer/Secretary, Peter Bruckner (peter.bruckner@uni-muenster.de).

Karl A. Piez (1924-2006): A Personal Tribute

Karl Piez was born in Needham, MA and served in the Army during World War II. He graduated from Yale University in 1947, received a Ph.D degree in Chemistry from Northwestern University in 1952, and joined NIDR (now NIDCR) shortly thereafter. He became chief of its Laboratory of Biochemistry in 1966. Karl retired from NIH in 1982 to become Chief Scientist and Director of Research at Collagen Corporation in Palo Alto, CA. Later on he was a founder and a member of the Board of Directors of FibroGen, Inc. a biotechnology company in South San Francisco, CA. In 1991, Karl returned to academia to become Professor of Biochemistry and Scholar-in-Residence at Jefferson University, School of Medicine. He retired in 1996.

During my first meeting with Karl in 1962, I was immediately struck by his enthusiasm for his work, his intelligence, candor, and sense of humor. Even though I was not particularly attracted to research on collagen at the time, I decided, on the spot, to work with him. Since, as an M.D., I had no previous experience in protein biochemistry, Karl carefully tutored me in the principles and practice of column chromatography, analytical ultracentrifugation, and amino acid analysis, pretty much the toolbox of collagen biochemists in those days. I then launched on an analysis of the chain composition of human skin collagen, which as Karl cleverly realized, allowed me to hold on to my clinical security blanket for a while longer. The results were pretty much the same as those previously published for rat collagen, but the paper was accepted by the JCI without revision – those were the days!

I remember the Piez lab at that time as a place of constant ferment, with exciting discussions among Karl, George Martin, and Ted Miller. Later, as we became more comfortable with the subject matter, Andy Kang, Bill Butler and I joined in. Two pressing questions in basic collagen chemistry were often debated. One related to the composition of collagen α chains. Karl favored a model in which the chains were generated by a continuous string of peptide bonds, whereas Paul Gallop, an accomplished organic chemist, was a prominent proponent of a model in which subunits were linked by ester bonds. The second question related to the chemical nature of the covalent inter-chain bonds that linked α chains to form β components, and that Karl suggested were related structurally and mechanistically to the intermolecular cross-links in collagen fibrils.

These discussions spurred me on to pursue experiments using CNBr to cleave purified α1 and α2 chains at methionyl bonds. Our rationale was that if repeating subunits existed in α chains, the pattern of CNBr-generated peptides should provide evidence for this claim. Furthermore, if we were lucky we might be able to isolate a cross-linked peptide from β_{12} components, and determine its structure. Karl and I discussed this approach at length. It was clear that he was not optimistic that it would succeed, but it was a mark of his superb mentorship that he was able to convey the problems that I might encounter without discouraging me. Karl's reservations were justified in that, initially, incomplete cleavage and poor separation of CNBr peptides made the interpretation of the results difficult. However, with the assistance of Andy Kang and Bill Butler, we were able to improve our chromatographic techniques and show that the CNBr fragmentation pattern was inconsistent with all of the subunit models under consideration. These experiments provided strong evidence for non-repetitive sequences in both the α1 and α2 chains. Furthermore, with a stroke of good fortune, we found that a single inter-chain covalent bond existed in a β_{12} component, and was located near the N-termini of the two α chain precursors, conveniently close to the first methionyl residues in the chains. Then, using collagen from both control rats, and lathyritic rats in which lysyl oxidase and cross-linking were inhibited, we proceeded to show that the interchain cross-link in β_{12} resulted from the interaction of a lysyl-derived aldehyde near the NH_2-terminus on one chain with a similar aldehyde on an adjacent chain to form an aldol condensation product. Later on, Karl's prediction that the mechanisms of formation of intramolecular and intermolecular cross-links were related was proven to be correct by the work of several other laboratories.

As exciting as these studies were for Andy Kang, Bill Butler, and me, Karl's lab was involved at the same time in equally significant studies that established the multiplicity of genetically distinct collagen types. Ted Miller showed, on the basis of analyses of CNBr-produced peptides, that cartilage contained a second structurally distinct protein, which was termed type II collagen, and shortly thereafter type III collagen was discovered in skin using similar techniques.

The field of matrix biology has made almost unimagined progress, as have other areas in biology, during the past 40 years. Nevertheless, those of us who work in areas of biology, medicine, and bioengineering, in which the biochemical and biophysical properties of collagen play an important role, owe a huge debt of gratitude to Karl Piez. For those of us who knew Karl personally, that debt is compounded by our appreciation of his human qualities: intelligence and intellectual rigor, tempered by kindness, generosity, and a fine sense of humor. In addition, for me, Karl's influence led to my career in matrix biology.

Paul Bornstein, Departments of Biochemistry and Medicine, University of Washington

Meeting Announcements

(see flyers for posting at the end of this issue)

The 20th Annual Meeting of the Japanese Society of Cartilage Metabolism
Okayama Convention Center, Okayama, Japan
March 2-3, 2007
Organizer: Yoshifumi Ninomiya, Okayama University
E-mail: nankotsu@md.okayama-u.ac.jp
www.t-inform.co.jp/jscm2006/

Gordon Research Conference "Cartilage Biology & Pathology"
Ventura Beach Marriott, Ventura, CA, USA
March 4-9, 2007
Chairs: Henry M. Kronenberg and Klaus C. von der Mark
Vice Chairs: Dick K. Heinegard and Bjorn R. Olsen
www.grc.org/programs.aspx?year=2007&program=cartbio

Joint Meeting of the Netherlands and German Connective Tissue Societies
Theme: "The Extracellular Matrix: Organiser of Biological Function"
University of Münster, Germany
March 8-10, 2007
ecm-meeting.klinikum.uni-muenster.de

Vascular Matrix Biology and Bioengineering Workshop
Whistler Village, British Columbia, Canada
March 15-18, 2007
Organised by Cecilia M. Giachelli and Michelle P. Bendeck
www.navbo.org/vascular_matrix_bio_workshop.dwt

Gordon Research Conference "Fibronectin, Integrins & Related Molecules"
Il Ciocco Barga, Italy
April 22-27, 2007
Chair: Dean Sheppard
Vice Chair: Fiona M Watt
www.grc.org/programs.aspx?year=2007&program=fibronec

Seventh International Conference on Hyaluronan
Frances Marion Hotel, Charleston, SC, USA
April 22-27, 2007
Sponsored by the International Society of Hyaluronan Sciences
Organised by Bryan P. Toole and Vincent C. Hascall

ASBMB 2007 Annual Meeting
Washington, DC, USA
April 28 - May 2, 2007
www.asbmb.org/ASBMB/site.nsf/Sub/2007AnnualMeeting?Opendocument

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 "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 "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 "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

XIIIth 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

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/

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

Matrix Research Update

In press publications

Collagen IX is indispensable for timely maturation of cartilage during fracture repair in mice
Alfred Opolka, Sabine Ratzinger, Thomas Schubert, Hans-Ulrich Spiegel, Joachim Grifka, Peter Bruckner, Axel Probst, Susanne Grässel
Matrix Biology

Fracture repair recapitulates in adult organisms the sequence of cell biological events of endochondral ossification during skeletal development and growth. After initial inflammation and deposition of granulation tissue, a cartilaginous callus is formed which, subsequently, is remodeled into bone. In part, bone formation is influenced also by the properties of the extracellular matrix of the cartilaginous callus. Deletion of individual macromolecular components can alter extracellular matrix suprastructures, and hence stability and organization of mesenchymal tissues. Here, we took advantage of the collagen IX knockout mouse model to better understand the role of this collagen for organization, differentiation and maturation of a cartilaginous template during formation of new bone. Although a seemingly crucial component of cartilage fibrils is missing, collagen IX-deficient mice develop normally, but are predisposed to premature joint cartilage degeneration. However, we show here that lack of collagen IX alters the time course of callus differentiation during bone fracture healing. The maturation of cartilage matrix was delayed in collagen IX deficient mice calli as judged by collagen X expression during the repair phase and the total amount of cartilage matrix was reduced. Entering the remodeling phase of fracture healing, *Col9a1*$^{-/-}$ calli retained a larger percentage of cartilage matrix than in wild type indicating also a delayed formation of new bone. We concluded that endochondral bone formation can occur in collagen IX knockout mice but is impaired under conditions of stress, such as the repair of an unfixed fractured long bone.

The NH_2-terminal propeptide of type I procollagen acts intracellularly to modulate cell function

Anush Oganesian, Sandra Au, Jeremy A. Horst, Lars C. Holzhausen, Athena J. Macy, James M.Pace, and Paul Bornstein

The Journal of Biological Chemistry

The function of the NH_2-terminal propeptide of type I procollagen (N-propeptide) is poorly understood. We now show that a recombinant trimeric N-propeptide interacts with TGFβ1 and BMP2 and exhibits functional effects in stably transfected cells. The synthesis of N-propeptide by COS-7 cells results in an increase in phosphorylation of Akt and Smad3, and is associated with a marked reduction in type I procollagen synthesis and impairment in adhesion. In C2C12 cells, N-propeptide inhibits the osteoblastic differentiation induced by BMP2. Our data suggest that these effects are mediated by the interaction of N-propeptide with an intracellular receptor in the secretory pathway, since they are not observed when recombinant N-propeptide is added to the culture medium of either COS-7 or C2C12 cells. Both the binding of N-propeptide to cytokines and its functional properties are entirely dependent on the exon 2-encoded globular domain, and a mutation that substitutes a serine for a highly conserved cysteine in exon 2 abolishes its function. Our findings suggest that N-propeptide performs an important feedback regulatory function and provide a rationale for the prominence of a homotrimeric form of type I procollagen (α1 trimer) during vertebrate development.

Collagen and Major Histocompatibility class II expression in mesenchymal cells from CIITA hypomorphic mice.

Yong Xu, Jessica McDonald, Emily Perloff, Giovanna Butticè, Barbara M. Schreiber and Barbara D. Smith

Molecular Immunology

Major histocompatibility class II (MHC II) transactivator (CIITA) is critical for interferon-gamma (IFN-gamma)-induced repression of collagen and activation of MHC II transcription. To better understand the role of CIITA and IFN-gamma-induced repression of collagen, mesenchymal cells, (lung fibroblasts, adventitial fibroblasts, and smooth muscle cells) were isolated from a CIITA deficient mouse ($C2ta^{tm1Ccum}$). IFN-gamma induced MHC II expression and repressed collagen type I expression in all three cell types isolated from the wild type background. As expected, IFN-gamma treatment of cells isolated from CIITA deficient mice did not induce MHC II production or activate the MHC II promoter. Interestingly, collagen gene expression and promoter activity was similar to that of wild type. Moreover, IFN-gamma induced CIITA mRNA and a truncated form of CIITA protein in all cells isolated from CIITA deficient mice. Most importantly, truncated CIITA occupied the collagen alpha 2(I) gene (col1a2) transcription start site during IFN-gamma treatment, but it did not occupy the MHC II promoter as judged by chromatin immunoprecipitation assays. Exogenous expression of a similar truncated form of CIITA maintained its ability to repress col1a2 transcription, but lost its ability to activate MHC II gene transcription suggesting a role for the CIITA C-terminal domain in activation, but not repression. IFN-gamma induced primarily type I and type IV CIITA isoforms in the mouse cells. All three isoforms of CIITA were capable of repressing col1a2 and activating MHC II gene transcription. These data suggest that the previously described CIITA knockout mouse carries a hypomorphic mutation, rather than a null mutation. The removal of the leucine rich region in CIITA blocks activation of MHC II without altering repression of collagen transcription.

Surviving ER stress is coupled to altered chondrocyte differentiation and function

Kwok Yeung Tsang, Danny Chan, Deborah Cheslett, Wilson C.W. Chan, Chi Leong So, Ian G. Melhado, Tori W.Y. Chan, Kin Ming Kwan, Ernst B. Hunziker, Yoshihiko Yamada, John F. Bateman, Kenneth M.C. Cheung & Kathryn S.E. Cheah

PLoS Biology

In protein folding and secretion disorders, activation of endoplasmic reticulum stress signaling (ERSS) protects cells, alleviating stress that would otherwise trigger apoptosis. Whether the stress-surviving cells resume normal function is not known. We studied the *in vivo* impact of ER stress in terminally differentiating hypertrophic chondrocytes (HCs) during endochondral bone formation. In transgenic mice expressing mutant collagen X as a consequence of a 13-bp deletion in *Col10a1 (13del)*, misfolded α1(X) chains accumulate in HCs and elicit ERSS. Histological and gene expression analyses showed that these chondrocytes survived ER stress but terminal differentiation is interrupted, endochondral bone formation is delayed, producing a chondrodysplasia phenotype. This altered differentiation involves cell-cycle re-entry, the re-expression of genes characteristic of a prehypertrophic-like state and is cell-autonomous. Concomitantly expression of *Col10a1* and *13del* mRNAs are reduced and ER stress is alleviated. ERSS, abnormal chondrocyte differentiation and altered growth plate architecture also occur in mice expressing mutant collagen II and aggrecan. Alteration of the differentiation program in chondrocytes expressing unfolded or misfolded proteins may be part of an adaptive response which facilitates survival and recovery from the ensuing ER stress. However the altered differentiation disrupts the highly coordinated events of endochondral ossification culminating in chondrodysplasia.

Job Advertisements

Post-doctoral Fellow in Functional Proteomics
(Ref.: RF-2006/2007-300)
THE UNIVERSITY OF HONG KONG

Applications are invited for appointment as Post-doctoral Fellow in Functional Proteomics in the Department of Biochemistry, tenable from as soon as possible, for a period of two years.

Applicants should have a Ph.D. degree in protein biochemistry and a good publication record. Experience in protein analysis using mass spectrometry would be an advantage. The appointee will work on proteomic analysis of abnormal chondrocyte differentiation in mouse mutants under the Area of Excellence programme of Developmental Genomics & Skeletal Research.

Applicants should submit a completed application form, and a curriculum vitae to the Department of Biochemistry, The University of Hong Kong, 3/F., Laboratory Block, Faculty of Medicine Building, 21 Sassoon Road, Pokfulam, Hong Kong. For details, please contact Professor K.S.E. Cheah at biochem@hkusua.hku.hk. Further information about the Department can be obtained at:
http://www.hku.hk/biochem/

A highly competitive salary commensurate with qualifications and experience will be offered.

The appointment carries leave, and medical/dental benefits.

Further particulars and application forms (272/302 amended) can be obtained at https://extranet.hku.hk/apptunit; by **fax** (2540 6735 or 2559 2058); **e-mail** (apptunit@hkucc.hku.hk); directly from the Appointments Unit, Room 1001, Knowles Building; or by **writing** to the Appointments Unit (Senior), Human Resource Section, Registry, The University of Hong Kong, enclosing a $1.40 stamped self-addressed envelope**. Closes: December 30, 2006.**

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Biomedical Research Associate in Osteoarthritis
Imperial College, London
Division of Medicine

Applications are invited for an aspiring scientist to work on a project funded by the Arthritis Research Campaign investigating the protective role of protease inhibitors in osteoarthritis. The candidate will participate in a collaborative project between Dr. George Bou-Gharios (Medicine) and Professor Hideaki Nagase (Kennedy Institute of Rheumatology). Specifically, the candidate will investigate the structural and biochemical changes in articular cartilage following OA induced models in vivo.

The successful post-holder will hold a BSc or equivalent and a PhD. A working knowledge and experience in histology and immunocytochemistry will be advantageous. This post is fixed term for three years and is based at the Hammersmith Hospital Campus located in East Acton, London, UK. Salary Range £23,560 - £28,930

For informal enquiries please contact Dr Bou-Gharios by emailing g.gharios@imperial.ac.uk.

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Post-Doctoral Position

Post doctoral position is available immediately for studies on: Inflammation in the central nervous system, in particular mechanisms of T-cell transmigration of blood vessels in mouse models of experimental autoimmune encephalitis. Work involves investigation of the role of extracellular matrix molecules, matrix metalloproteinases and chemokines on T-cell extravasation, and T-cell signal transduction pathways. See Sixt et al., J. Cell Biol. **153**, 933-945, 2001, and Agrawal et al., J Exp Med **203**, 1007-10019, for details.

Candidates should submit a full CV to Dr Lydia Sorokin, Institute of Biochemistry and Pathobiochemistry, Muenster University, Waldeyerstr. 15, D-48149 Muenster, Germany, sorokin@uni-muenster.de

Please include full contact information for three references. Applications lacking references will not be considered. We thank you in advance for your interest. Only those applicants selected for an interview will be contacted.

Responsible Newsletter Editors

Jamie Fitzgerald: fitzgerj@ohsu.edu
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From the Editor's Desk

Dear readers of Matrix Biology,

If one were to list what currently is "in" or "out" in biomedical science, it would be difficult to avoid placing "stem cells" and associated terms such as "niche", "microenvironment" and "lineage specification" high up on the "in" list. Anyone in doubt is referred to PubMed, where a quick search for articles on "stem cells" identifies 10 times more items than a search for "osteoblasts". While many, perhaps the majority, of these stem cell papers are likely to have a short half-life, some recent publications are truly significant contributions that deepen our understanding of how stem cell differentiation is controlled.

One such is by Takahashi and Yamanaka (Takahashi and Yamanaka, 2006) who report that a combination of transcription factors, when introduced into mouse embryonic or adult fibroblasts, can induce de-differentiation of the cells to a pluripotent stem cell-like state. Based on their previous work and the work of others on genes that appear to contribute to maintenance of pluripotency, Takahashi and Yamanaka tested 24 genes as candidates for molecules that could induce pluripotency in somatic cells. The investigators developed a screening assay for pluripotency that makes clever use of a gene, Fbxl5, specifically expressed in mouse embryonic stem (ES) cells and in early embryos.

In previous studies, the investigators have found that Fbx15 is a target of a transcription factor (Oct 3/4) that is important for maintenance of ES cell pluripotency, and that inactivation of Fbxl5 has no effect on pluripotency and embryonic development (Tokuzawa et al., 2003). ES cells that carry a cassette encoding a fusion of β-galactosidase and the neomycin resistance gene (βgeo) inserted into the Fbx15 locus are therefore pluripotent and can support normal mouse development. In addition, since they express the neomycin resistance gene, they are also highly resistant to culture in the presence of high concentrations of the drug G418.

Embryonic fibroblasts from mice generated with G418-resistant Fbx15$^{\beta geo}$ ES-cells and grown under conditions normally used for ES cell culture, produced no G418-resistant colonies when the cells were transfected (by retroviral transfer) with each of the 24 selected test genes, but generated several resistant colonies when they were transfected with a mixture of all 24 candidates. Many of these resistant colonies contained cells with ES-cells like morphologies and doubling times; RT-PCR analyses indicated that they expressed several markers for ES cells. In further studies, Takahashi and Yamanaka removed individual factors from the pool of 24 candidates and finally arrived at a short list of four genes, Oct 3/4, Klf4, Sox2 and c-Myc, that together could induce mouse embryonic fibroblasts to activate the modified Fbx15$^{\beta geo}$ locus and become resistant to G418.

Using DNA microarrays to compare gene expression profiles of wild-type ES cells, Fbx15$^{\beta geo/\beta geo}$ mouse embryonic fibroblasts and the induced ES-like cells (called iPS cells), the investigators could show that iPS cell transcripts cluster closely with ES cells; additional expression data showed that iPS cells and ES cells are very similar, although not identical. Further assays, including teratoma formation in nude mice and formation of embryoid bodies in tissue culture, confirmed that iPS cells induced with the 4-factor "gene cocktail", are pluripotent like control ES cells. The investigators also introduced the 4 factors into fibroblasts from the tails of 2-3 months old male and female mice, isolated G418-resistant iPS clones and demonstrated that they could form tumors with all three germ layers in nude mice. In addition they introduced iPS clones, generated from adult tail fibroblasts and expressing green fluorescent protein (GFP), into blastocysts and found that iPS cells contributed to all three germ layers in the resulting embryos. Finally, the investigators found that iPS cells, unlike ES cells, do not remain undifferentiated in the presence of LIF without feeder cells. This finding, plus differences in gene expression patterns between iPS cells and ES cells, makes it unlikely that the iPS clones represent contamination of pre-existing ES cells.

These are intriguing results that will undoubtedly stimulate further work in many laboratories. One obvious question that needs to be addressed is that of whether the pluripotent iPS cells are derived from transfection of fully differentiated fibroblasts or whether they represent dedifferentiation of less differentiated mesenchymal progenitor cells in the fibroblast cultures. Takahashi and Yamanaka provide several arguments in favor of the conclusion that the small number of resistant colonies generated in the experiments may not be a reflection of reprogramming of a minor precursor population of cells, but only further experiments will be able to definitively answer the question. Another result of the study that may stimulate further work is the observation that Nanog appears to be dispensable, although it is one of the transcription factors (Oct 3/4, Sox2 and Nanog) that are currently considered critical core factors for maintenance of pluripotency in ES cells (Boyer et al., 2005; Loh et al., 2006). Given the demonstrated role of Nanog in supporting self-renewal of stem cells (Chambers et al., 2003; see also (Olsen, 2003)), this is unexpected.

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Takahashi and Yamanaka are careful to point out that they do not know whether the 4 transfected factors they found to be sufficient for generation of pluripotent clones from mouse fibroblasts, can generate pluripotent cells also from human somatic cells. Nevertheless, their study opens the door to a better understanding of molecular mechanisms that control pluripotency. To think that such understanding one day will allow induction of pluripotent cells from somatic cells of patients, no longer seems like the unrealistic, science fiction dream it was a few short years ago.

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B.R. Olsen

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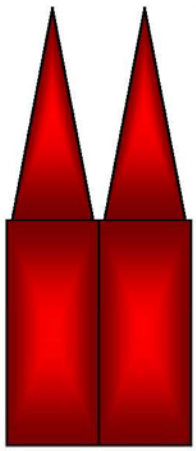

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The Extracellular Matrix: Organiser of Biological Function

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March 8th – 10th, 2007 in Münster, Germany

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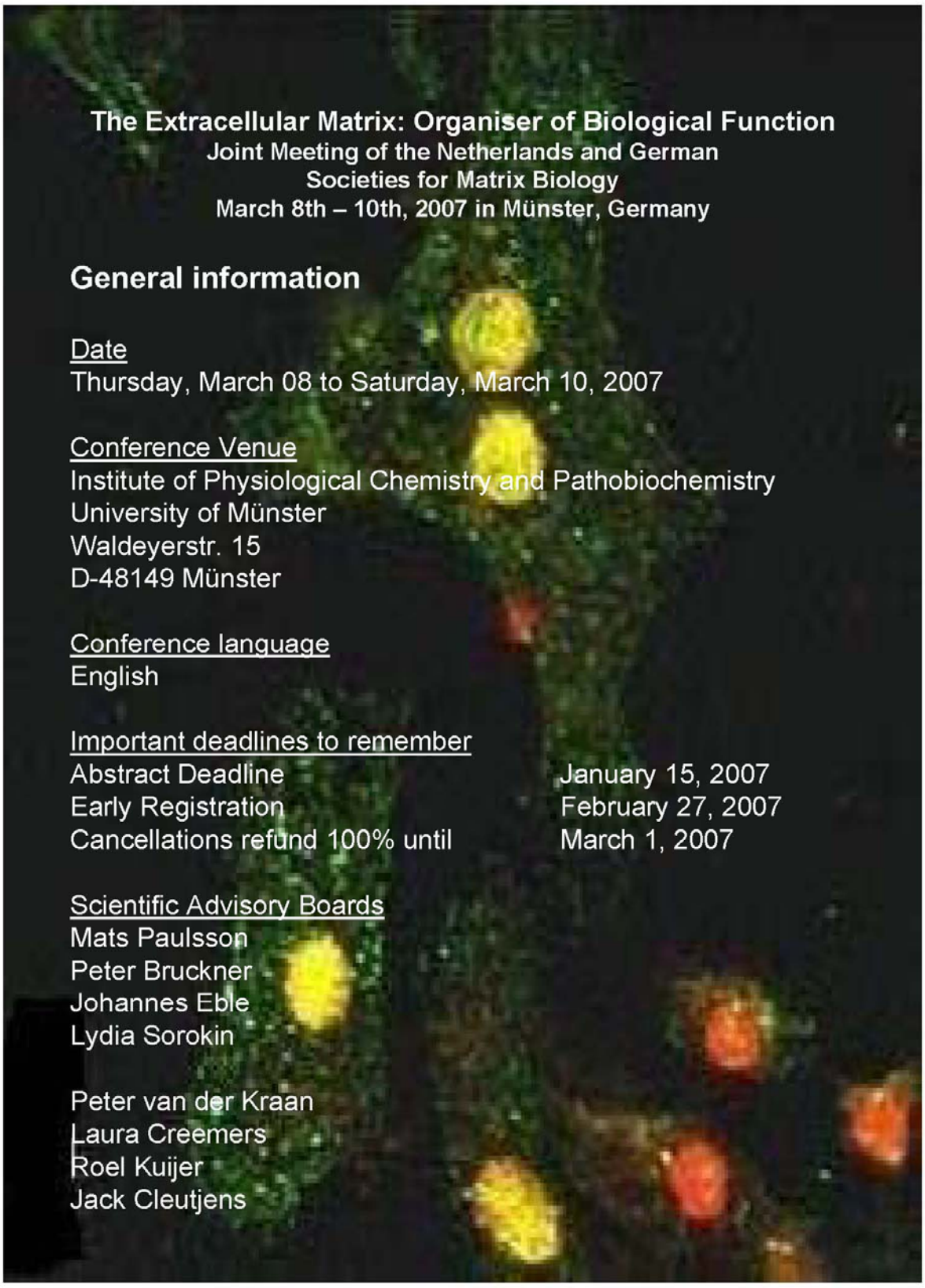
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March 8th – 10th, 2007 in Münster, Germany
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