International Society for Matrix Biology Newsletter

No. 8 - April 2008

Contents

From the President's Desk

Dear ISMB members,

Greetings! Council is very happy to have much to report in this newsletter. ISMB continues to reach out and link matrix biologists world-wide by facilitating international participation at the meetings of national matrix biology societies. This year we will be facilitating international networking and promoting excellence in matrix biology at the FECTS and ASMB meetings through travel awards for junior investigators and prizes.

7th PPCTS Symposium in association with ISMB 2007

ISMB's flag flew high at this meeting. Several of us Council members, Dieter Reinhardt, John Bateman, Yasunori Okada and myself, were able to attend the meeting and are happy to report on a very successful meeting with quality talks and great interactions at the edge of the Great Barrier Reef in Cairns! Our awardees Sue McGlashan at the University of Auckland, New Zealand and Tony Poole at the University of Otago, New Zealand (ISMB-*Matrix Biology* 2006/2007 Best Paper Award), Dr. Zhongjun Zhou of the University of Hong Kong (ISMB Speaker) and Dr. Takashi Ogawa of Kihara Institute for Biological Research, Yokohama City University (ISMB New Investigator Award) gave great talks which stimulated good discussions. Yoshihiro Ishikawa at the Shriners Hospital for Children, Portland, OR and Kyoto University, Japan won the ISMB–*Matrix Biology* Best Student Poster Award. See the pictures of the celebrating awardees below!

Partnership with FECTS: FECTS 2008 Symposium in association with ISMB

ISMB will once again be participating in the FECTS Symposium. To help young scientists to participate the ISMB is offering 3 travelling fellowships of 500 € each for non European PhD students and post-docs. The successful recipients will be selected from the abstracts and they will deliver short talks. ISMB will also be recognising research excellence through the award of the Rupert Timpl ISMB prize. The winner will be delivering a lecture at the symposium. Watch this space for announcement of the winner in the next Newsletter!

Partnership with the American Society of Matrix Biology: Awards and prizes for ASMB 2008 meeting

Once again with the generous support of *Matrix Biology*, there will be ISMB-*Matrix Biology* poster prizes and travel awards for PhD students and junior investigators (up to 10 years postdoc experience, but not yet an independent group leader). There will be an ISMB special session in which the recipient of the ISMB Distinguished Investigator Prize (see below) will give a special plenary lecture and short presentations will be made by the winners of the travel awards.

ISMB Distinguished Investigator Prize Winner – Reinhard Fässler

Thank you all of you who nominated candidates for the first ISMB award for excellence in research in matrix biology in the period 2005-2007. We received nominations for an outstanding list of eight candidates and after close voting by Council members, we are proud to announce that Reinhard Fässler will be the first recipient of the prize. Reinhard, pictured right, will deliver the First ISMB Distinguished Investigator Prize lecture at the upcoming ASMB meeting in December 2008 in San Diego. Congratulations to Reinhard and we look forward to a splendid lecture!!

ISMB Logo Competition

The ISMB council received a total of six different designs as suggestions for the new ISMB logo. The council members selected one of them provided by the artist Angela McQuillan, pictured left, in Renato Iozzo's lab at Thomas Jefferson University. Congratulations to Angela for the 100 Euro prize. Renato generously turned down the second part of the prize, which would have been a one year free ISMB membership.

Membership

We are happy to see some improvements in our membership numbers and especially the number who have paid their dues!! But we need to recruit more members so we can continue to facilitate the international networking of matrix biologists and maybe do even more. So please do bang the drum for ISMB, help us recruit new members.

Until the next time, please continue to help keep the ISMB flag flying high!! All good wishes for continued success in your research.

Kathy Cheah
President, ISMB

Meeting Announcements

Canadian Connective Tissue Conference 2008

Montreal, Canada
June 5 – 7, 2008
Chairs: Dieter Reinhardt and Mari Kaartinen
E-mail: dieter.reinhardt@mcgill.ca;
mari.kaartinen@mcgill.ca
http://cctc2008.mcgill.ca

Basement Membranes Gordon Research Conference

University of New England, Maine (near Boston)
June 22-27th, 2008
Chair: Jeffrey Miner
Vice-chair: Monique Aumailley
This will be the fourteenth in a highly successful series of biannual meetings that have been major international forums for dissemination of new concepts regarding the structure and function of basement membranes. The 2008 Conference will present a diverse mixture of sessions on basement membrane protein structure, biosynthesis, assembly, and function during development and in disease. In addition to invited speakers, **there will be numerous opportunities for oral presentations by graduate students, postdocs, and junior faculty based on submitted abstracts**. Additional information is available at www.grc.org.

Gordon Research Conference Proteoglycans

Andover, NH, Proctor Academy
July 6-11, 2008
Chair: Thomas N. Wight
Vice Chair: Marian F. Young
Additional information is available at http://www.grc.org/programs.aspx?year=2008&program=proteoglyc

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
http://www.fects2008.pharmacie.univ-mrs.fr/

Invited speakers
Sunneel APTE (Cleveland, USA)
Yann BARRANDON (Lausanne (Suisse)
Antony DAY (Manchester, UK)
Holger GERHARDT (London, UK)
Marie-Madeleine GIRAUD-GUILLE (Paris, France)
Eckhard LAMMERT (Dresden, Germany)
Birgit LEITINGER (London, UK)
Robert MECHAM (St Louis, USA)
Stefan MUNDLOS (Berlin, Germany)
Johanna MYLLYHARJU (Oulu, Finland)
Tomoyuki NAKAMURA (Kyoto, Japan)
Chris OVERALL (Vancouver, Canada)
Mario RASPANTI (Varese, Italy)
Florence RUGGIERO (Lyon, France)

Workshop topics:
Cell-matrix interactions and signalling, Dynamic aspects of the ECM, ECM and cancer, ECM and development, ECM diseases and therapies, ECM: from inside the cell to the matrix, ECM: from molecules to extracellular machines, ECM maturation and aging, ECM: source and reservoir of bioactive molecules, Metalloproteinases:

remodelling of the extracellular matrix and cell surface, Stem cells, Systems biology, Tissue engineering: from the lab to the patient, Vascular Biology and angiogenesis

5th European Elastin Meeting 2008
Alcala de Henares (near Madrid), Spain
July 16-19, 2008
Chair: Julia Bujan
http://www.elastin2008.fgua.es/info/info.cfm?lang=i

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

Gordon Research Conference Biomineralization
New London, NH, Colby-Sawyer College
August 10-15, 2008
Chair: James J. De Yoreo
Vice Chair: Lia Addadi
Additional information is available at
http://www.grc.org/programs.aspx?year=2008&program=biomin

American Society for Matrix Biology 2008 meeting
San Diego, CA, USA
December 7-10, 2008
Chair: Bill Parks
Program details can be found at:
www.asmb.net/2008meeting/.
Online registration is now open

Workshop: Vascular Matrix Biology and Bioengineering II
Whistler, British Columbia, Canada
March 16-19, 2009
Chairs: Cecilia Giachelli and Michelle Bendeck
michelle.bendeck@utoronto.ca

Matrix Research Update

Papers in press

Three novel collagen VI chains with high homology to the α3 chain

Sudheer Kumar Gara, Paolo Grumati, Anna Urciuolo, Paolo Bonaldo, Brigit Kobbe, Manuel Koch, Mats Paulsson and Raimund Wagener

Journal of Biological Chemistry

Here we describe three novel collagen VI chains, alpha4, alpha5, and alpha6. The corresponding genes are arranged in tandem on mouse chromosome 9. The new chains structurally resemble the collagen VI alpha3 chain. Each chain consists of seven von Willebrand factor A domains followed by a collagenous domain, two C-terminal von Willebrand factor A domains, and a unique domain. In addition, the collagen VI alpha4 chain carries a Kunitz domain at the C terminus, whereas the collagen VI alpha5 chain contains an additional von Willebrand factor A domain and a unique domain. The size of the collagenous domains and the position of the structurally important cysteine residues within these domains are identical between the collagen VI alpha3, alpha4, alpha5, and alpha6 chains. In mouse, the new chains are found in or close to basement membranes. Collagen VI alpha1 chain-deficient mice lack expression of the new collagen VI chains implicating that the new chains may substitute for the alpha3 chain, probably forming alpha1alpha2alpha4, alpha1alpha2alpha5, or alpha1alpha2alpha6 heterotrimers. Due to a large scale pericentric inversion, the human COL6A4 gene on chromosome 3 was broken into two pieces and became a non-processed pseudogene. Recently COL6A5 was linked to atopic dermatitis and designated COL29A1. The identification of novel collagen VI chains carries implications for the etiology of atopic dermatitis as well as Bethlem myopathy and Ullrich congenital muscular dystrophy.

Three novel collagen VI chains, α4(VI), α5(VI) and α6(VI).

Jamie Fitzgerald, Cathleen Rich, Fiona Zhou and Uwe Hansen

Journal of Biological Chemistry

We report the identification of three new collagen VI genes at a single locus on human chromosome 3q22.1. The three new genes are COL6A4, COL6A5 and COL6A6 that encode the α4(VI), α5(VI) and α6(VI) chains. In humans, the COL6A4 gene has been disrupted by a chromosome break. Each of the three new collagen chains contain a 336 amino acid triple helix flanked by seven N-terminal von Willebrand factor A-like-domains (VWA-domains) and two (α4 and α6 chains) or three (α5 chain) C-terminal VWA-domains. In humans, mRNA expression of COL6A5 is restricted to a few tissues including lung, testis and colon. In contrast, the COL6A6 gene is expressed in a wide range of fetal and adult tissues including lung, kidney, liver, spleen, thymus, heart and skeletal muscle. Antibodies to the α6(VI) chain stained the extracellular matrix of human skeletal and cardiac muscle, lung and the territorial matrix of articular cartilage. In cell transfection and immunoprecipitation experiments, mouse α4(VI)N6-C2 chain co-assembled with endogenous α1(VI) and α2(VI) chains to form trimeric collagen VI molecules that were secreted from the cell. In contrast, α5(VI)N5-C1 and α6(VI)N6-C2 chains did not assemble with α1(VI) and α2(VI) chains and accumulated intracellularly. We conclude that the α4(VI)N6-C2 chain contains all the elements necessary for trimerization with α1(VI) and α2(VI). In summary, the discovery of three additional

collagen VI chains doubles the collagen VI family and adds a layer of complexity to collagen VI assembly and function in the extracellular matrix.

Evidence for articular cartilage regeneration in MRL/MpJ mice

Jamie Fitzgerald, Cathleen Rich, Dan Burkhardt, Justin Allen, Andrea Herzka and Chris Little.

Osteoarthritis and Cartilage

Objective. A major clinical problem in Orthopaedics is the repair of traumatic articular cartilage lesions. The MRL/MpJ strain of mice has the remarkable ability to regenerate ear hole punch wounds seamlessly including the scarless replacement of multiple tissues. The objective of this study was to assess whether articular cartilage defects repair or regenerate in the MRL/MpJ 'healer' strain of mice.

Method. Full thickness and partial thickness lesions were introduced into trochlear groove articular cartilage of MRL/MpJ and C57Bl/6 mice, a control strain that does not undergo ear hole regeneration. The wound sites were assessed 6-wks and 12-weeks post-surgery using a histological scoring scheme and immunohistochemistry for markers of articular cartilage including proteoglycan, collagen II and collagen VI.

Results. The partial thickness lesions did not repair in either strain. However, at both 6-wk and 12-wk timepoints the MRL/MpJ mice had a superior healing response of full thickness lesions with abundant chondrocytes and an extracellular matrix rich in proteoglycan, collagen II and collagen VI at the wound site. At the 12-wk timepoint the enhanced cartilage healing was restricted to male MRL/MpJ mice. In contrast, the C57Bl/6 control strain produced an extracellular matrix at the wound site that, overall, had significantly less matrix proteoglycan and collagen II.

Conclusions. Male MRL/MpJ mice appear to possess an intrinsic ability to 'regenerate' articular cartilage. Understanding the biochemical and genetic basis for articular cartilage regeneration may open up new treatment options for traumatic articular cartilage defects.

Liquid Crystallinity in Collagen Systems *in vitro* and *in vivo*

Marie Madeleine Giraud-Guille, Gervaise Mosser, Emmanuel Belamie

Current Opinion in Colloid and Interface Science

Collagens are unique triple helical proteins present in large quantities in a fibrillar form in tissues like tendon, bone, skin, cornea, where type I collagen predominates. The passage from triple helical molecules to fibrils obeys to controlled assembly properties, both *in vitro* by pH raise and *in vivo* through enzymatic control. The passage from individual fibrils to ordered fibrillar arrays could rely on self-assembly processes as suggested by the liquid crystalline properties of collagen. The present review considers this question recalling the liquid crystalline ordering properties of collagen or procollagen at high concentrations and the question of molecular packing within fibrils. The presence of alignments, undulations and twist at a suprafibrillar level will be described both from basic data in living tissues and recent experiments in self-assembled materials. The possible link between laboratory experiences and biological processes will be discussed.

Characterization and functional analysis of osteoblast-derived fibulins in the human hematopoietic stem cell niche

Sonja Hergeth, Wilhelm Aicher, Mike Essl,Thomas Schreiber, Takako Sasaki and Gerd Klein

Experimental Hematology

Objective: In the bone marrow stem cell niche, osteoblasts lining the endosteum are of major importance in supporting hematopoietic stem cell maintenance. Our objective was to analyze the expression of the fibulins, highly conserved calcium-binding glycoproteins which are components of the extracellular matrix of human osteoblasts, and to provide insights into their functional interactions with hematopoietic progenitor cells.
Methods: Expression of the fibulins by human osteoblasts was determined by RT-PCR analysis and by immunofluorescence staining and immunoblotting using fibulin-specific antisera. Recombinant fibulins were used in cell proliferation and differentiation assays with human CD34+ hematopoietic progenitor cells. Adhesive interactions of CD34+ cells with fibulins were investigated using cell adhesion assays.

Results: Human osteoblasts strongly express and secrete fibulin-1 and -2. Whereas fibulin-1 is secreted in its intact form, fibulin-2 synthesized by human osteoblasts undergoes rapid proteolytic degradation. The gelatinase MMP-2, which is constitutively expressed by the osteoblasts, seems to be responsible for fibulin-2 degradation. Fibulin-1 showed an inhibitory effect on short-term CD34+ hematopoietic progenitor cell proliferation. Both fibulin-1 and fibulin-2 were able to diminish erythroid and myeloid colony formation. The CD34+ cell line KG1a strongly attached to fibulin-2, whereas MACS-sorted CD34+ hematopoietic progenitors did not adhere to either fibulin-1 or fibulin-2. On the other hand, fibulin-1 can strongly interfere with CD34+ cell adhesion to fibronectin.

Conclusion: Fibulins seem to be important components of the extracellular matrix of osteoblasts and are likely to negatively influence the proliferation rate of stem cells and the overall adhesive properties of the endosteal stem cell niche.

Biogenesis of extracellular microfibrils - Multimerization of the fibrillin-1 C-terminus into bead-like structures enables self-assembly

D, Hubmacher, E.I. El-Hallous, V. Nelea, M.T. Kaartinen, E.R. Lee, D.P. Reinhardt

Proceedings of the National Academy of Sciences

Microfibrils are essential elements in elastic and non-elastic tissues contributing to homeostasis and growth factor regulation. Fibrillins form the core of these multi-component assemblies. Various human genetic disorders, the fibrillinopathies, arise from mutations in fibrillins and are frequently associated with aberrant microfibril assembly. These disorders include Marfan syndrome, Weill-Marchesani syndrome, Beals syndrome and others. While homotypic and heterotypic fibrillin self-interactions are considered to provide critical initial steps, the detailed mechanisms for microfibril assembly are unknown. We show here that the C-terminal recombinant half of fibrillin-1 assembles into disulfide-bonded multimeric globular structures with peripheral arms and a dense core. These globules are similar to the beaded structures observed in microfibrils isolated from tissues. Only these C-terminal fibrillin-1 multimers interacted strongly with the fibrillin-1 N-terminus, whereas the monomers showed very little self-interaction activity. The multimers strongly inhibited microfibril formation in cell culture providing evidence that these recombinant assemblies can also interact with endogenous fibrillin-1. The C-terminal self-interaction site was fine mapped to the last three calcium-binding EGF domains in fibrillin-1. These results suggest a new mechanism for microfibril formation where fibrillin-1 first oligomerizes via its C-terminus before the partially or fully assembled bead-like structures can further interact with other beads via the fibrillin-1 N-termini.

Proteomic characterization of cartilage degradation *in vitro.*

Wilson, R., Belluoccio, D., Little, C.B., Fosang, A.J. and Bateman, J.F.

Arthritis and Rheumatism

Objective. To develop and validate proteomic methodologies for the analysis of cartilage degradation in the mouse, and to correlate transcriptional and translational responses to catabolic stimuli *in vitro*.

Methods. Proteomic techniques were used to analyze the products and outcomes of cartilage catabolism in mouse femoral head explants. We developed specific methods to prepare cartilage extracts and conditioned media for resolution by two-dimensional polyacrylamide gel electrophoresis (2-D PAGE) and subsequent protein identification by tandem mass spectrometry (MS). Cartilage degradation was induced by treatment of mouse cartilage explants with interleukin-1α (IL-1) or all-*trans*-retinoic acid (RetA) and differential SDS-PAGE and 2-D PAGE analysis were used to identify novel proteins and protein fragments released into the media of control and treated explants. In addition we used fluorescent difference gel electrophoresis (2-D DIGE) of multiplexed IL-1 *vs* control and RetA *vs* control conditioned media samples to quantify treatment-induced protein expression changes. Changes in the mRNA expression for the differentially abundant proteins were also analyzed to differentiate between transcriptional and post-translational regulation of protein release.

Results. Proteomic characterization of femoral head cartilage by 2-D PAGE and tandem MS generated a 2-D reference map for mouse cartilage comprising 56 proteins, glycoproteins and proteoglycans. We identified 27 proteins in the culture media of non-stimulated cartilage explants, including a novel perlecan fragment. Differential profiling of conditioned media from control, IL-1 and RetA-treated explants resulted in the identification of 20 differentially-abundant proteins, including proteolytic fragments of thrombospondin-1 and connective tissue growth factor. The majority of IL-1 and RetA-induced changes in protein abundance and protein fragmentation were treatment specific. IL-1 stimulated the release of well-known markers of cartilage degeneration, such as MMP-3, as well as proteins with uncharacterized roles in cartilage pathology, such as neutrophil gelatinase-associated lipocalin. The major response of mouse cartilage to RetA treatment was the release of ECM components such as cartilage oligomeric matrix protein, link protein and matrilin-3 into the media, accompanied by a dramatic reduction in levels of the corresponding mRNA transcripts. Gelsolin, a protein implicated in cytoskeletal reorganization in arthritic synovial fibroblasts but not previously associated with cartilage pathology, was regulated by IL-1 and RetA.

Conclusions. We have applied quantitative and qualitative proteomics to characterize an explant culture system using mouse cartilage and analyze the response of mouse cartilage to catabolic stimuli. Several of the released products in explant culture media, including both fragmented and intact proteins, represent novel candidate biomarkers for cartilage degradation. Applying these differential proteomic techniques to wild-type and genetically modified mouse cartilage will lead to further insight into pathological mechanisms involved in cartilage degeneration.

Recently in print

Serglycin – Structure and Biology

Svein Kolset and H Tveit

Cellular and Molecular Life Sciences

Serglycin is a proteoglycan found in hematopoietic cells and endothelial cells. It has important functions related to formation of several types of storage granules. In connective tissue mast cells the covalently attached glycosaminoglycan is heparin, whereas mucosal mast cells and activated macrophages contain oversulfated chondroitin sulfate (type E). In mast cells, serglycin

interact with histamine, chymase, tryptase and carboxypeptidase, in neutrophils with elastase, in cytotoxic T cells with granzyme B, in endothelial cells with tissue-type plasminogen activator and in macrophages with tumor necrosis factor-alpha. Serglycin is important for the retention of key inflammatory mediators inside storage granules and secretory vesicles. Serglycin can further modulate the activities of partner molecules in different ways after secretion from activated immune cells, through protection, transport, activation and interactions with substrates or target cells. Serglycin is a proteoglycan with important roles in inflammatory reactions.

The extracellular matrix protein WARP is a novel component of a distinct subset of basement membranes

Justin M. Allen, Bent Brachvogel, Peter G. Farlie, Jamie Fitzgerald and John F. Bateman

Matrix Biology

WARP is a recently described member of the von Willebrand factor A domain superfamily of extracellular matrix proteins, and is encoded by the Vwa1 gene. We have previously shown that WARP is a multimeric component of the chondrocyte pericellular matrix in articular cartilage and intervertebral disc, where it interacts with the basement membrane heparan sulfate proteoglycan perlecan. However, the tissue-specific expression of WARP in non-cartilaginous tissues and its localization in the extracellular matrix of other perlecan-containing tissues have not been analyzed in detail. To visualize WARP-expressing cells, we generated a reporter gene knock-in mouse by targeted replacement of the Vwa1 gene with beta-galactosidase. Analysis of reporter gene expression and WARP protein localization by immunostaining demonstrates that WARP is a component of a limited number of distinct basement membranes. WARP is expressed in the vasculature of neural tissues and in basement membrane structures of the peripheral nervous system. Furthermore, WARP is also expressed in the apical ectodermal ridge of developing limb buds, and in skeletal and cardiac muscle. These findings are the first evidence for WARP expression in non-cartilaginous tissues, and the identification of WARP as a component of a limited range of specialized basement membranes provides further evidence for the heterogeneous composition of basement membranes between different tissues.

Thrombospondins Use the VLDL Receptor and a Nonapoptotic Pathway to Inhibit Cell Division in Microvascular Endothelial Cells

Anush Oganesian, Lucas C. Armstrong, Mary M. Migliorini, Dudley K. Strickland, and Paul Bornstein

Molecular Biology of the Cell

TSPs 1 and 2 function as endogenous inhibitors of angiogenesis. Although thrombospondins (TSPs) have been shown to induce apoptosis in HMVECs, we reasoned that a homeostatic mechanism would also be needed to inhibit EC growth without causing cell death, e.g., in the maintenance of a normal vascular endothelium. HMVECs, cultured in low serum, responded to VEGF with an increase in [3H]thymidine incorporation that was inhibited by TSPs and was accompanied by decreases in the phosphorylation of Akt and MAPK, without an increase in apoptosis. RAP, an inhibitor of the low-density lipoprotein (LDL) family of endocytic receptors, and blocking antibodies to VLDLR were as effective as TSPs in the inhibition of thymidine uptake in response to VEGF, and the effects of these agents were not additive. Supportive evidence for the role of the VLDLR in mediating this inhibition was provided by the demonstration of a high-affinity interaction between TSPs and the VLDLR. We propose that TSP1 and TSP2, together with the VLDLR, initiate a nonapoptotic pathway for maintenance of the normal adult vascular endothelium in a quiescent state, similar to that invoked for the regulation of mitogenesis by PDGF, but involving signaling via the VLDLR rather than LRP1.

Proteomic profiling of endorepellin angiostatic activity on human endothelial cells.

Zoeller, JJ and Iozzo, RV

Proteome Science

A central function for perlecan in skeletal muscle and cardiovascular development

Zoeller JJ, McQuillin AM, Whitelock J, Ho S-Y and Iozzo RV

Journal of Cell Biology

Dear Fellow Matrix Biologists, I thought you would be interested in two new research reports from our laboratory. Recently we embarked on a proteomics approach to examine the anti-angiogenic influence of perlecan's C-terminal domain V/endorepellin on endothelial cells. Our investigations identified five key proteins, calreticulin, Hsp60, beta-actin, vimentin and prolyl 4-hydroxylase, beta-subunit, which represent potential target areas involved with endorepellin mechanism of action. All of these proteins have been implicated in angiogenesis (Zoeller JJ and Iozzo RV, Proteome Science 2008 6:7). Another key focus area in our lab involves the fascinating zebrafish, Danio rerio. We characterized perlecan in the zebrafish for the first time and identified a central role for perlecan in somitic muscle development and developmental angiogenesis. This work establishes perlecan as a key regulator of angiogenic sprouting likely involving VEGF/VEGFR2 signaling pathway and predicts a key role for perlecan in human myopathy/muscle dystrophy (Zoeller JJ, et al, Journal of Cell Biology In Press 2008) I am delighted to share these works with the community and hope you find them of great interest. Best personal regards.
Renato V. Iozzo, M.D., Vice-president ISMB

ISMB Membership news

Are you by any chance among those many who still have not yet renewed their memberships for 2008? Better late than never. Please take out your VISA- or Master/Euro-Card and go to http://www.ismb.org. You will find directions under “Membership” on how to proceed. It is simple. If you are the proud owner of a credit card and also have access to the internet there is simply no excuse for you. It is as safe as any other SSL-encoded transaction that you may conduct over the internet.

To best serve the matrix biology community it is important to keep our membership details up-to-date. Please let us know if you change email address or regular mailing address. Please email Jamie Fitzgerald (fitzgerj@ohsu.edu) and Peter Bruckner (peter.bruckner@uni-muenster.de) with any address changes so we can update our records.

In memoriam **Wolfgang F. Vogel**

We were recently saddened by the news of the sudden passing of Professor Wolfgang Vogel, University of Toronto. Wolfgang Vogel was in the prime of his life and with his sudden death the field of matrix biology has lost a prominent young scientist.

Wolfgang studied Chemistry in Freiburg, Germany, and received his PhD in molecular biology from the University of Munich in 1994. He carried out his graduate student studies in Axel Ullrich's laboratory working on kinase-regulated mechanisms. During this period he published his first paper on a particular family of kinases which, at that time, contained orphan receptors and were later named the discoidin domain receptor family (DDRs). But it was later, during a very productive postdoc period in Tony Pawson's laboratory at the University of Toronto (1995-1999) that Wolfgang established DDRs as collagen receptors. This was the start of 10 successful years of research elucidating the structure and function of DDRs.
After a short sojourn (1999-2001) as junior group leader in Frankfurt, Wolfgang returned to Toronto in 2001 to the Department of Laboratory Medicine and Pathobiology where he was recently awarded tenurship.

After having established that DDRs bind collagens, several years of exciting science followed; animals deficient in DDRs were generated, their phenotypes were studied and, thereby, different aspects of DDR structure and function were defined. Wolfgang Vogel was always intimately associated with the work on DDRs and his name will always be linked with discoidin domain receptors. Some of us had the privilege to hear Wolfgang speak at a recent Collagen Gordon Conference outside Boston in the summer of 2007, where he presented the latest data in the field in a plenary lecture. During the same conference we enjoyed hours of stimulating discussions on collagen receptors, red wine and a pleasant summer afternoon canoeing along one of the small rivers in the area. Only two weeks ago Wolfgang visited his family in Germany and spent time visiting many of us to discuss collaborative projects and to make ambitious plans for the future.

We will remember Wolfgang as an enthusiastic scientist and a fair and conscientious collaborator. In simple words, he was "a very nice guy", open and friendly, energetic and positive. He will be missed both for his excellent science and his lovely personality. We extend our deepest sympathies his wife, Vanita, and his parents and family.

Beate Eckes, Johannes Eble, Oliver Gross and Donald Gullberg

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

From the Editor's Desk

How to keep that stemmy-ness: Stem cells in the spotlight

Dear readers of Matrix Biology,

During the last few years, the buzz around stem cells has been ever-increasing (in 2007 just below, 12,000 articles dealing with stem cells were published). This is also reflected in the editorial pages of Matrix Biology where the network of transcription factors needed to maintain pluripotency has been discussed (Olsen, 2006). I like to review some recent papers dealing with various aspects of stem cells, including the identification of an extracellular network that maintains the pluripotency of human embryonic stem cells.

When growing embryonic stem cells (ES) in the laboratory, one often relies on a layer of fibroblasts, called the feeder cells. These produce factors that retain the pluripotency of the stem cells. Recent proteomic approaches to define proteins released by feeder cells have revealed large differences in secreted proteins between mouse embryonic fibroblasts and two types of human fibroblasts (Prowse et al., 2007). This stresses the point that fibroblasts are different. The increasing awareness that fibroblasts are heterogeneous, even within tissues, was clearly illustrated in a recent study reporting clonal variation of fibroblasts isolated from the skin (Sorrell et al., 2007). Returning to the factors that maintain pluripotency, in the case of mouse ES cells the important factors have been identified as leukemia inhibitory factor (LIF) and bone morphogenetic proteins (BMPs) (Ying et al., 2003).

With the increased interest in stem cell therapy, substantial efforts have been made to define cell culture media for human stem cells so that they become free from animal products (i.e. proteins derived from non-human feeder cells and bovine serum). In the case of human embryonic stem cells it was known that FGF-2 could replace the feeder cell layer, but exactly how FGF-2 was accomplishing the maintenance of stem cell pluripotency (also referred to as stemness or stemmy-ness) was not, until recently, known.

In an elegant paper from Bendall et al. the detailed mechanism of FGF-2 action on human embryonic stem cells was studied (Bendall et al., 2007). Their work shows that part of the stem cells differentiates to form fibroblast-like cells that then serve the function of establishing a stem cell niche. This is to say that in the absence of a feeder cell layer the stem cells make their own feeder cells. These fibroblast-like cells are shown to respond to FGF-2 by secreting IGF-II and TGF-beta which both act to maintain pluripotency and prevent ES cell differentiation (Fig. 1).

The ES cells are distinguished from the fibroblast-like cells by their FGF and TGF-β receptor expression patterns, i.e. ES cells express the relevant IGF receptors and fibroblast-like cells express FGF receptors. This extracellular paracrine network thus acts to set up the stem cell-like niche. The cell-matrix aspect of this niche remains to be explored.

In another recent publication the cell adhesion aspect of the stem cell niche has been explored using the *Drosophila* system. When studying the role of integrins for testis formation, it was found that integrins act to correctly position the germ stem cells within the testis (Tanentzapf et al., 2007; Van Doren, 2007).

An extrapolation from the fruit fly to humans would suggest that maybe in the future one needs to make sure that stem cells being transplanted have the correct integrin repertoire in order to "take" at the right place in the tissue. One might have to engineer stem cells with different integrin repertoires to optimize take rates in different tissues.

Finally, a stem cell paper published late last year has already become controversial. The group of Robert Weinberg has made significant contributions to cancer biology. In the paper of Karnoub et al. they report the establishment of a model to study tumor metastasis in a xenograft model (Karnoub et al., 2007). Two controversial findings from the study are that stem cells are recruited to the tumors, and as a result of bi-directional signaling

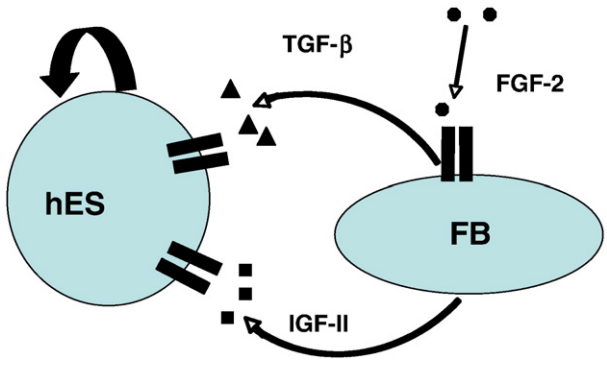

Fig. 1. Paracrine network in human embryonic stem cell cultures where fibroblasts-like cells (FB) respond to FGF-2 by secreting TGF-β and IGF-II, which act to retain the stemness of the human embryonic stem cells (hES).

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with the tumor cells, the stem cells secrete CCL5, which promotes metastasis. The metastasis is thus not a result of a mutation in the stem cells, but is caused by a re-training of the tumor cells by the secreted cytokine from the stromal stem cells. The validity of stem cells contributing to tumor metastasis by secreting CCL5 remains to be shown in humans. Also in these models the cell-matrix aspect of these events remains to be characterized.

In the years to come stem cells will play increasingly important roles in regenerative medicine and other stem cell-based therapies. In addition to understanding the nuclear transcriptional networks and the extracellular paracrine networks by which stem cells communicate and respond to the host tissue, it will be important to understand the cell adhesion aspect of these interactions.

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ISMB Award winners announced at the 7th Pan Pacific Connective Tissue Societies Symposium in Cairns, Australia (28th October - 1st November 2007)

ISMB-*Matrix Biology* 2006/2007 Best Paper Award (US$1000)
Sue McGlashan (University of Auckland, New Zealand) and
Tony Poole (University of Otago, New Zealand)

"*Articular cartilage and growth plate defects are associated with chondrocyte cytoskeletal abnormalities in Tg737orpk mice lacking the primary cilia protein polaris*"
S.R. McGlashan, C.J. Haycraft, C.G. Jensen, B.K. Yoder, C.A. Poole
Matrix Biology, 26:234–246, 2007

ISMB New Investigator Award
to an investigator within 5 years of PhD
Takashi Ogawa
(Yokohama City University, Japan)
(to the right of Kathy Cheah, ISMB President)
Value: $US 500

ISMB Lecture
Zhongjun Zhou
(University of Hong Kong)
Value: $US 500

ISMB-*Matrix Biology* Best Student Poster Award
Yoshihiro Ishikawa
(Shriners Hospital for Children, Portland, OR, USA
and Kyoto University, Japan)
Value: $US 500

UNIVERSITY OF OTAGO
Te Whare Wananga o Otago
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Postdoctoral Fellowship

Department of Medical and Surgical Sciences
Section of Orthopaedic Surgery

We seek a talented post-doctoral candidate with research experience in mechanobiology, including cell signalling pathways, connective tissue biology and real-time calcium imaging. The Marsden funded research to be completed over three years involves biomechanical and biochemical studies on the function of primary cilia in kidney cells. We require skills in cell and tissue culture, molecular analysis and live cell imaging, and some familiarity with a dynamic cell-loading system would be an advantage. A strong understanding of cell biology and the role of primary cilia in mechanosensation will be essential. The prime function of the research is use *in vitro* culture techniques to examine the influence of primary cilia expression on the biomechanical and physiological responsiveness of mutant and wild-type fibroblast cell lines. The appointee will be expected to develop cell culture techniques using the Flexercell cell straining system to examine the influence of mechanical strain on the proliferative, synthetic and calcium signalling capacity of normal ciliated and mutant non ciliated fibroblasts under mechanically strained and unstrained conditions. The individual appointed will be directly responsible to Associate Professor Tony Poole, Section of Orthopaedic Surgery, Department of Medical and Surgical Sciences, Dunedin School of Medicine.

Specific enquiries may be directed to Associate Professor C.A. (Tony) Poole, Section of Orthopaedic Surgery, Department of Medical and Surgical Sciences, Dunedin School of Medicine, Dunedin. Phone: 03 474 0999 ext 8613. Email tony.poole@stonebow.otago.ac.nz

Closing Date: Open

APPLICATION INFORMATION
With each application you must include an application form, an EEO Information Statement, a covering letter, contact details for three referees and one copy of your full curriculum vitae. **For an application form, EEO Information Statement and a full job description go to: *www.otago.ac.nz/jobs*** Alternatively, contact the **Human Resources Division, Tel 03 479 8269, Fax 03 479 8279, Email** *job.applications@otago.ac.nz*

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Postdoc Position

A postdoc position is available for addressing the question of how the tumor matrix molecule tenascin-C is promoting cancer. Cell biological and biochemical experiments and a transgenic tumor model will be used to determine the angiogenesis and metastasis promoting effect of ectopically expressed tenascin-C at the mechanistic level.

The Tumor-Stroma laboratory was founded in 2002 at the University of Basel, Center of Biomedicine, and has recently been translocated to the Inserm U682 in Strasbourg, which is part of the University of Strasbourg and of the CRBS (Centre de Recherche en Biomédicine de Strasbourg, which will house 23 groups in the center of Strasbourg and is implemented in 2009, http://crbs.u-strasbg.fr). The current team members are from Germany, China and France. Excellent core-facilities and equipment are available in a challenging and stimulating scientific atmosphere.

If you are a highly motivated and independent researcher holding a PhD with experience in cell biology and are willing to work in an international setting in beautiful Strasbourg, you are welcome to address **Gertraud Orend** at ***gertraud.orend@inserm.u-strasbg.fr***.




PD Dr. rer. nat. Gertraud Orend

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