



# International Society for Matrix Biology Newsletter

No. 2 - January 2006

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## From the President's Desk

I hope you all had a happy and safe Holiday Season and New Year, and on behalf of the ISMB Council I wish you success in your research, and a personally fulfilling 2006. For ISMB, 2006 brings a year of changes, challenges and hopefully a significant role in fostering and supporting matrix biology.

### ***Changes – Call for Nominations ISMB Council***

Many of the current Council Members complete their terms this year, including my term as President. The other completing Council Members are Ruth Chiquet-Ehrismann, Benoit de Crombrughe, Dick Heinegård, Martin Humphries, Renato Iozzo, Gerard Karsenty, Mats Paulsson, Taina Pihlajaniemi, Lydia Sorokin, Jouni Uitto, Michel van der Rest, Zena Werb, Kenneth Yamada and Peter Yurchenco. We will be emailing members for nominations for Council shortly, with the ballot to held after a short-list is established and biographical information on the candidates sent out to ISMB members. Current Council Members may be re-nominated. So, please have a think about possible candidates and canvass your colleagues. The position of Vice-President is currently vacant, so both the Vice-Presidency and Presidency will also be elected by members from a slate of candidates to be put forward by Council.

### ***Rupert Timpl Award***

The "Rupert Timpl Award" will be made in conjunction with the 2006 FECTS meeting. The award is made every two years and is based on the "best paper" on a subject in matrix biology published by a young scientist in the preceding two years. The closing date for nominations for the 2006 award is April 30, 2006 and papers published in 2004 and 2005 will be considered. Submissions should be made to Peter Bruckner [[peter.bruckner@uni-muenster.de](mailto:peter.bruckner@uni-muenster.de)].

### ***Matrix Biology – "From the Editor's Desk"***

For the past three years, Bjorn Olsen has written illuminating and thought-provoking articles on many aspects of matrix biology. In the latest addition of *Matrix Biology* (December, 2005), Bjorn has invited readers to "... help make these Editorial pages a place where both you and I can share with colleagues and friends our ideas and fascination with discoveries in matrix biology. Beginning with the next issue, I would like to be able to publish letters and comments from readers as well as guest editorials in addition to my own communications". I encourage ISMB members to take advantage of this opportunity and support Bjorn in his endeavours to provide a range of diverse views and perspectives on our field of matrix biology. Further details on the suggested content and style of these guest "From the Editor's Desk" contributions can be found in Bjorn's editorial in the December issue of *Matrix Biology*.

### ***Contributions to the Newsletter***

I have been gratified by the emails from members expressing enthusiasm about the re-initiation of an ISMB Newsletter. However, the Newsletter Editors have indicated to me that they have not been exactly overwhelmed by contributions from members, as yet. I urge members to let Jamie and Dieter know about jobs, scholarships and the like. This newsletter should provide you with an opportunity to publicise these to a broader audience. Likewise, please consider submitting the details of your latest accepted publications, so that this research is brought to the attention of interested peers in the "Matrix Research Update" section.

Again, best wishes for 2006 and I look forward to catching up with many of you at the FECTS/ISMB meeting in Oulu this July.

Regards,  
John Bateman

### **Meeting Announcements**

#### ***Gordon Research Conference "Plasminogen Activation & Extracellular Proteolysis"***

This conference will be held in Harbortown Ventura, CA, USA from February 19-24, 2006. Conference website: <http://www.grc.org/programs/2006/plasmino.htm>.

#### ***Annual Meeting of the German Connective Tissue Society***

This meeting will be held in Tübingen, Germany from March 9-11, 2006. Conference website: <http://www.wewe-design.de/dgfb2006/>.

#### ***Gordon Research Conference "Fibroblast Growth Factors in Development & Disease"***

This conference will be held in Harbortown Ventura, CA, USA from March 12-17, 2006. Conference website: <http://www.grc.org/programs/2006/fibro.htm>.

#### ***Gordon Research Conference "Basement Membranes"***

This meeting will be held in Il Ciocco, Italy from June 18-23, 2006. Conference website: <http://www.grc.org/programs/2006/basement.htm>

### ***The XXth meeting of the Federation of European Connective Tissue Societies***

Arranged jointly with the **International Society of Matrix Biology** in Oulu, Finland on July 1-5, 2006. Registration for the meeting is now open at the web site <http://www.facts-ismb.org>.

### ***4th European Meeting on Elastin***

This conference will be held in Lyon, France from July 9-12, 2006. Conference website: <http://www.ujf-grenoble.fr/BIO/elastin2006/>.

### ***Gordon Research Conference "Proteoglycans"***

This conference will be held in Andover, NH, USA from July 9-14, 2006. Conference website: <http://www.grc.org/programs/2006/protglyc.htm>.

### **Matrix Research Update**

#### ***In Press Publications***

**WARP is a novel multimeric component of the chondrocyte pericellular matrix that interacts with perlecan**

J.M. Allen, J.F. Bateman, U. Hansen, R. Wilson, P. Bruckner, R.T. Owens, T. Sasaki, R. Timpl and J. Fitzgerald [[j.fitzgerald@mcri.edu.au](mailto:j.fitzgerald@mcri.edu.au)]

#### ***Journal of Biological Chemistry***

WARP is a novel member of the von Willebrand factor A-domain superfamily of extracellular matrix proteins that is expressed by chondrocytes. WARP is restricted to the presumptive articular cartilage zone prior to joint cavitation and to the articular cartilage and fibrocartilaginous elements in the joint, spine and sternum during mouse embryonic development. In mature articular cartilage, WARP is highly specific for the chondrocyte pericellular microenvironment and co-localizes with perlecan, a prominent component of the chondrocyte pericellular region. WARP is present in the guanidine-soluble fraction of cartilage matrix extracts as a disulfide-bonded multimer indicating that WARP is a strongly interacting component of the cartilage matrix. To investigate how WARP is integrated with the pericellular environment, we studied WARP binding to mouse perlecan using solid phase and surface plasmon resonance analysis. WARP interacts with domain III-2 of the perlecan core protein and the heparan sulfate chains of the perlecan domain I with KD values in the low nanomolar range. We conclude that WARP forms macromolecular structures that interact with perlecan to contribute to the assembly and/or maintenance of 'permanent' cartilage structures during development and in mature cartilages.

### **Fibrillin-1 regulates mesangial cell attachment, spreading, migration and proliferation**

M. Porst, C. Plank, B. Bieritz, E. Konik, H. Fees, J. Dötsch, K. F. Hilgers, D. P. Reinhardt, and A. Hartner [[andrea.hartner@rzmail.uni-erlangen.de](mailto:andrea.hartner@rzmail.uni-erlangen.de)]

#### *Kidney International*

**Background:** The microfibrillar protein fibrillin-1 is present in many organs including the vasculature, eye and dermis and is thought to convey structural anchorage and elastic strength. Fibrillin-1 is also a component of the mesangial matrix. To assess the functional relevance of fibrillin-1 for cell-matrix interactions in the glomerulus, we studied attachment, spreading, migration and proliferation of mesangial cells on fibrillin-1 and the regulation of fibrillin-1 in experimental anti-Thy1.1 nephritis displaying mesangial cell migration and proliferation in vivo.

**Methods:** Adhesion of mesangial cells was studied by a hexosaminidase-based attachment assay on fibrillin-1 fragments: RGD-containing fibrillin-1 fragment (rF6H) and one fibrillin-1 fragment lacking the RGD-site (rF16). Focal contacts were detected by immunostaining for vinculin. Migration was assessed by a transmigration assay and proliferation was measured by a BrdU incorporation assay. In glomeruli of experimental Thy1.1 nephritic rats, Fibrillin-1 mRNA and protein expression was assessed.

**Results:** During the acute phase of experimental Thy1.1 nephritis, glomerular fibrillin-1 mRNA expression and protein immunoreactivity was significantly induced as compared to controls. Mesangial cells showed concentration-dependent attachment to the fibrillin-1 fragment rF6H, similar to what was observed for fibronectin, but not to fragment rF16. The cell attachment was RGD dependent. Further, fragment rF6H significantly promoted spreading, focal contact formation, cell migration and proliferation of mesangial cells.

**Conclusion:** We conclude that fibrillin-1 promotes mesangial cell attachment, spreading, migration and proliferation and could thus contribute to mesangial hypercellularity during glomerular disease.

### **Characterization of a laminin-5 containing conduit system in the human thymus - a transport system for small molecules.**

M. Drumea-Mirancea, J. T. Wessels, C. A. Müller, M. Essl, J. A. Eble, M. Tolosa, M. Koch, D. P. Reinhardt, M. Sixt, L. Sorokin, Y.-D. Stierhof, H. Schwarz, and G. Klein [[gerd.klein@uni-tuebingen.de](mailto:gerd.klein@uni-tuebingen.de)]

#### *Journal of Cell Science*

T-cells develop in the thymus in a highly specialized cellular and extracellular microenvironment. The basement membrane molecule, laminin-5 (LN-5), is predominantly found in the medulla of the human thymic lobules. Using high resolution light microscopy, we show here that LN-5 is localized in a bi-

membranous conduit-like structure, together with other typical basement membrane components, including collagen type IV, nidogen and perlecan. Other interstitial matrix components, like fibrillin-1 or -2, tenascin-C or fibrillar collagen types, were also associated with these structures. 3D-confocal microscopy suggested a tubular structure, while immunoelectron and transmission electron microscopy showed that the core of these tubes contained fibrillar collagens enwrapped by the LN-5 containing membrane. These medullary conduits are surrounded by thymic epithelial cells, which in vitro were found to bind LN-5, but also fibrillin and tenascin-C. Dendritic cells were also detected in close vicinity to the conduits. Both of these stromal cell types express MHC class II molecules capable of antigen presentation. The conduits are connected to blood vessels, but with an average diameter of 2 µm they are too small to transport cells. Smaller molecules such as a 10 or 70 kDa dextran but not large molecules (>500 kDa) are readily transported in the conduits. These results clearly demonstrate that a conduit system, which is also known from secondary lymphatic organs such as lymph nodes and spleen, is present in the medulla of the human thymus, and that it may serve for the transport of small blood-borne molecules or chemokines to defined locations within the medulla.

### **Job Advertisements**

**Studentships** (2) are available at Department of Biomedicine, Division of Physiology, University of Bergen, Norway.

Projects are offered in matrix biology related to regulation of proteoglycan synthesis (group of Marion Kusche Gullberg [[marion.kusche@biomed.uib.no](mailto:marion.kusche@biomed.uib.no)]) or to function of collagen-binding integrins (group of Donald Gullberg [[donald.gullberg@biomed.uib.no](mailto:donald.gullberg@biomed.uib.no)]). For a description of projects please go to the home page at: <http://www.uib.no/med/biomed/research/gullberg/>.

Candidates with background in physiology, molecular biology, cell biology or biochemistry will be considered. Experience with glycobiology (MKG) or molecular biology/cell biology (DG) is a merit. The positions are initially available for one year, and are restricted to nationals of EU nations. After one year the possibility to extend the studentships to graduate studies will be evaluated. Please send CV, 3 letters of recommendations to Donald Gullberg at: Department of Biomedicine, Division of Physiology, University of Bergen, Jonas Lies vei 91, 5009 Bergen, Norway, at the latest January 30th, 2006.

### **Responsible Newsletter Editors**

Jamie Fitzgerald: [j.fitzgerald@mcri.edu.au](mailto:j.fitzgerald@mcri.edu.au)

Dieter Reinhardt: [dieter.reinhardt@mccgill.ca](mailto:dieter.reinhardt@mccgill.ca)

## From the Editor's Desk

Dear readers of *Matrix Biology*,

Nearly all cells in vertebrates and many cells in invertebrates contain primary cilia. Except for the motile nodal cilia in vertebrates (essential for establishment of left-right asymmetry) primary cilia are non-motile structures on interphase cells containing 9 pairs of microtubules running under the plasma membrane from the basal body to the tip of the cilium. They grow and are maintained by intraciliary/intraflagellar transport of protein complexes. These complexes are assembled around the basal body at the root of the cilium and are transported into and out of the cilium between the microtubules and the plasma membrane.

Primary cilia were first described more than 100 years ago (Zimmerman, 1898), but except for the modified cilia in retinal photoreceptors, cilia on olfactory epithelial cells, and the mechano-sensory cilia in the inner ear, they remained for a long time somewhat of an orphan organelle in cell biology—a curiosity of obscure function. This situation has changed dramatically in the past few years and primary cilia are now recognized as sensory organelles for detection and transmission of mechanical and chemical information from the extracellular environment of cells. For example, bending of the cilium on kidney epithelial cells by fluid flow results in an increase in intracellular  $\text{Ca}^{++}$  (Praetorius and Spring, 2001), mediated by a channel located at the base of the cilium and composed of the transmembrane proteins PC1 and PC2 (Nauli et al., 2003). In fruit flies, an auditory organ of the second antennal segment contains primary cilia extending from the tips of sensory neuron dendrites; displacement of the cilia by vibrations trigger potentials in the neurons (Martinez-Campos et al., 2004).

Several types of receptors are known to be transported into and localized in primary cilia. These include odorant receptors in *C.elegans* (Dwyer et al., 2001), the G protein-coupled somatostatin receptor 3 in neuronal cilia of mice and rats (Handel et al., 1999) and the serotonin receptor 5-HT6 in rat brain neuronal cilia (Brailov et al., 2000). Of particular interest to matrix biologists is the localization of  $\beta$ 1-integrins to the primary cilia of MDCK cells and rat renal proximal tubule and collecting duct cells (Praetorius et

al., 2004). These strong hints that cilia may function as sensors of ligand-receptor interactions at some distance away from the cell body, have recently received a terrific boost by the demonstration that vertebrate Smoothed (Smo), the hedgehog (Hh) signaling receptor, also functions at the primary cilium. Using two polyclonal antibodies against Smo, Corbit et al. (2005) have demonstrated that Smo is located predominantly on primary cilia in ventral node cells of early mouse embryos. In experiments with MDCK cells that constitutively express Myc-tagged murine Smo, these authors found that incubation of the cells in the presence of Sonic hedgehog (Shh) induced an upregulation of the amount of ciliary Smo. In contrast, incubation of the cells with the Shh antagonist cyclopamine eliminated Smo from the primary cilium! An activated mutant mouse Smo, SmoA1, was found to be strongly localized in the cilium, even in the absence of Shh. To demonstrate that Shh also affects Smo localization to primary cilia *in vivo*, Corbit et al. (2005) cultured mouse embryos in the presence of cyclopamine and observed a decreased localization of Smo to primary cilia.

Dwyer et al. (2001) have reported that the transport of odorant proteins into primary cilia of *C.elegans* neurons requires the presence of a hydrophobic and basic amino acid residue motif immediately downstream of their seventh transmembrane segment, and a similar motif is present in the ciliary receptors somatostatin 3 and serotonin receptor 5-HT6. One can imagine the excitement Corbit et al. (2005) must have felt when they realized that Smo also contains such a sequence downstream of its seventh transmembrane domain, and discovered that a Smo-Myc protein with this motif replaced by alanine residues failed to localize to cilia, even in the presence of Shh and in spite of the fact that the mutant protein was expressed on the cell plasma membrane and in intracellular vesicles. Thus, this motif may be a ciliary localization motif that is shared by a number of ciliary transmembrane receptors.

To address the question of whether the ciliary localization of Smo is required for its function as a Shh signaling molecule, Corbit et al. (2005) transfected NIH-3T3 cells containing a Gli-dependent luciferase reporter of Shh

signaling with wild-type and mutant Smo. Cells transfected with wild-type Smo exhibited an almost 20-fold increase in luciferase activity; in contrast, mutant SmoA1 did not stimulate activity above the levels of the control. Finally, Corbit et al. compared the function of wild-type and mutant Smo in zebrafish and found that the ciliary localization motif was required for Smo function also in this organism.

These exciting results do not address the question of why Smo must be localized to the primary cilium for proper function. However, they do provide an explanation for several recent observations that have led to the conclusion that ciliary transport proteins and components are required for hedgehog signaling. In a screen for embryonic patterning mutations induced by ethylnitrosourea, Huangfu et al. (2003) identified two mouse mutants, *wim* and *fxo*, that exhibit abnormalities in dorso-ventral patterning of the neural tube as well as other phenotypes resembling those seen as a consequence of defects in Shh signaling. *Fxo* is a hypomorphic allele of the ciliary protein polaris and *wim* is a mutant allele of another ciliary protein that is part of a complex with polaris. Polaris mutants (Zhang et al., 2003) have limb patterning defects consistent with defects in hedgehog signaling, in addition to abnormalities in left-right asymmetry and polycystic kidney disease, and Liu et al. (2005) have recently reported that *fxo* mutants have polydactyly in all four limbs. Although Shh expression is normal in early *fxo* limbs, molecular analyses suggest that Gli proteins, known targets of hedgehog signaling, are insensitive to hedgehog in the absence of intraflagellar proteins such as polaris (Liu et al., 2005).

And the story does not stop here. In a recent follow-up study to their 2003 paper, Huangfu and Anderson (2005) add to the excitement by demonstrating that motor proteins required for the anterograde and retrograde transport of proteins into and out of cilia are essential for both the positive and negative responses to hedgehog signaling that are mediated by Gli proteins. Consistent with their conclusion that “cilia act as organelles that are required for all activity of the mouse Hh pathway”, conditionally mutant mice, in which a subunit (Kif3a) of the kinesin II anterograde motor has been inactivated in early limb or in neural crest-derived craniofacial mesenchyme exhibit limb skeletal and craniofacial defects that are practically identical to those caused by mutations in Shh signaling components (Olsen et al., 2005).

These studies will undoubtedly lead to an assessment of the ciliary contribution to many other ligand-receptor triggered signaling pathways in vertebrate cells. Given the number of different kinds of receptors that already have

been found to be localized in cilia, it would not be surprising to see this 100 year-old cellular organelle become the focus of the most intense scrutiny and excitement in the next few months and years. What's in it for matrix biologists? Mesenchymal cells, fibroblasts, chondrocytes, osteoblasts and odontoblasts all have primary cilia. Do I need to say more?

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