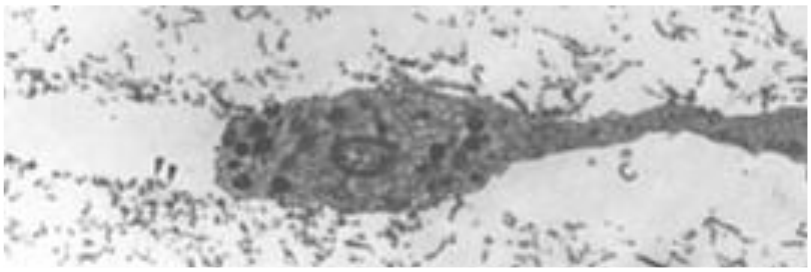


A fibroblast within a tethered lattice, after 13 days, with a cavity surrounding the cell and areas of packed collagen fibrils *(Porter et al. 1998 Wound Rep. Reg. 6: 157-166)*

ISMB NEWSLETTER 41 May 2022 Editor: Sylvie Ricard-Blum

FROM THE PRESIDENT'S DESK

Dear Fellow Matrix Biologists:

Greetings from Cleveland, Ohio. Here, summer arrived rather suddenly after it seemed it never would. That's made it somewhat harder to stay in the office and lab, but perhaps my work will have a sharper focus with the possibility of getting outside to enjoy the fine days as a motivation. I am hoping for some time in the White Mountains of New Hampshire in the week before the Proteoglycan Gordon Conference, and I hope those of you in the northern hemisphere will have an enjoyable summer as well, with relaxing vacations, time with friends and family and stimulating science thrown in now and then in just the right dose.

As usual, Sylvie has done a stellar job with the newsletter, which reports several in-person conferences to look forward to (at last!!). The most important thing to relate to these is the possibility for student and post-doc members to apply for international travel grants, one of the principal reasons for the existence of ISMB and also one of the main uses of membership dues. The newsletter reports exciting new developments in the matrix field and we encourage more submissions from ISMB members for inclusion. There is also the sad news of the passing of Klaus Kuhn. The remembrances underscore his enormous scientific legacy and stress the positive impact we can all have as mentors to early career scientists, now and in the future.

Please join me in welcoming Julia Etich, University of Cologne, Germany, as the new ISMB Secretary. Thank you to Julia for taking on this important position. Julia replaces John Whitelock, who will step down as Secretary to devote more time and effort to his role as Editor-in-Chief of Matrix Biology and Matrix Biology Plus. A very hearty Thank You is due to John for his work as ISMB Secretary. Finally, we very much hope ISMB members will continue to submit quality articles to both journals.

Best wishes

Suneel Apte, President of the ISMB (aptes@ccf.org)

Content

New Council members

Professor Qing-Jun Meng (MD & PhD), Versus Arthritis Senior Research Fellow, Director of Internationalisation (School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester). He is the "Chrono-Matrix" Theme Leader of the Wellcome Centre for Cell-Matrix Research, Bursary Chair of the British Society for Matrix Biology, Co-director and Board of the Wellcome Trust Immuno-Matrix in Complex Diseases (ICD) PhD program.

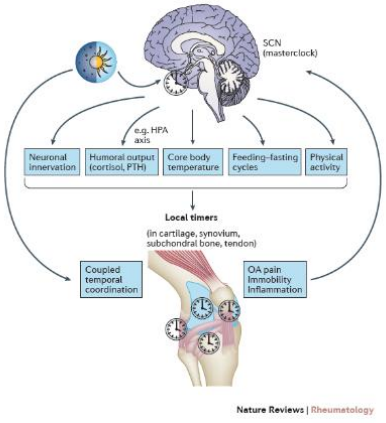
Qing-Jun started his post-doctoral training on circadian clocks at the University of Manchester in 2003. In 2009, he received a five-year MRC Career Development Fellowship Award to start his independent group. This was followed by a Versus Arthritis Senior Research Fellowship Award in 2015. He was promoted to a Professor of Chronobiology in 2017. His earlier research has contributed to the understanding of the molecular clocks and their pharmacological regulation (Neuron 2008; Curr Bio 2010; PNAS 2010; Nucleic Acids Res 2014). His current interest is the interface between circadian biology, extracellular matrix homeostasis and age-related diseases, including osteoarthritis (Arthritis & Rheum 2013; Osteo & Cartilage 2015/2021; JCI 2016; Theranostics 2022), intervertebral disc degeneration (Annals Rheum Dis 2017; Bone Res 2022), fibrosis and tendinopathies (Genes & Dev 2014; Sci Rep 2014; Nat Cell Bio 2020) and breast cancer (Nat Comms 2017; J Cell Sci 2018; Breast Cancer Res 2018). He has received research funding from the MRC, BBSRC sLoLa, Wellcome Trust, Versus Arthritis, Breast Cancer Now and industries (GSK and Walgreens Boots Alliance). His research profile has received extensive media coverage including BBC Breakfast, BBC Radio Stoke, BBC Radio 5, BBC Radio Manchester.

Key publications (* co-corresponding authors):

1) Chang J, Garva R, Pickard A, Yeung C-YC, Mallikarjun V, Swift J, Holmes DF, Calverley B, Lu Y, Adamson A, Raymond-Hayling H, Jensen O, Shearer T, Meng*QJ and Kadler*KE (2020). Circadian control of the secretory pathway maintains collagen homeostasis. **Nat Cell Biology**, 22, 74.

2) Yang N, Williams J, Pekovic-Vaughan V, Wang P, OlabiS, McConnell J, Gossan N, Hughes A, Cheung J, Streuli* CH & Meng*QJ (2017). Cellular mechano-environment regulates the mammary circadian clock. **Nat Comms.** 8,14287.

3) Dudek M, Yang N, Ruckshanthi JP, Williams J, Borysiewicz E, Wang P, Adamson A, Li J, Bateman JF, White MR, Boot-Handford RP, Hoyland*JA & Meng*QJ (2017). The intervertebral disc contains intrinsic circadian clocks that are regulated by age and cytokines and linked to degeneration. **Annals Rheum Dis.** 76, 576. Highlighted by Nat Rev Rheum: Catching the rhythm of disc degeneration.



4) Dudek M, Gossan N, Yang N, Im HJ, Ruckshanthi JPD, Yoshitane H, Li X, Jin D, Wang P, Boudiffa M, Bellantuono I, Fukada Y, Boot-Handford* RP and Meng* QJ (2016). Thechondrocyte clock gene Bmal1 controls cartilage homeostasis and integrity. **J Clin Invest.** 126, 365. Cover Story| Highlighted by Nat Rev Rheum: Chondrocyte clock maintains cartilage tissue.

Obituary

In memory of

Prof. Dr. Dr. h.c. Klaus Kühn

**1.5.1927 † 8.4.2022*

Klaus Kühn was a pioneer in collagen research with landmark discoveries in the collagen field, who shaped a sustainable extracellular matrix research in Germany and throughout the world. The passionate collagen scientist was fascinated by the collagen tripelhelix and was always a leading, highly motivating figure in the field who encouraged generations of young people to climb apparently unsurmountable summits. Somehow, it happened that every chair in matrix biology research in Germany came from or went through Klaus Kühn's lab. The German Society for Matrix Biology and the worldwide matrix biology community is greatly saddened by the passing of Klaus Kühn.

Klaus Kühn had managed to establish an extremely successful international research center while maintaining a kind and collegial atmosphere within the department, welcoming students and scientists from all over the world. This was unique in the highly hierarchical academic structure in Germany at that time. Klaus Kühn was proud to be a typical chemist but he welcomed initiatives to approach connective tissue research from many different angles and he was always very interested in medical issues. He enjoyed scientific discussions as well as playing tennis with the members of his department. There is no doubt that he had a profound influence on our scientific, academic and personal life.

Monique Aumailley and Thomas Krieg

Klaus Kühn leaves behind for us a memory to an impressive and generous scientist personality who was always modest and kind. In addition to his landmark scientific contributions on the structure and function of collagens, his accomplishments include the fostering and support of a large number of scientists whose development and careers he influenced in a decisive way. We all owe him our gratitude for this.

Peter Bruckner

Er war ein ausgezeichneter Lehrmeister, der wissenschaftliche Expertise mit einer fürsorglichen Menschlichkeit verband. Unvergesslich ist, wie er junge Wissenschaftler in die Wissenschaftsgemeinde der Extrazellulären Matrix integrierte. Der offene Wissenschaftsaustausch und die angenehme Umgebung auf Matrix-Tagungen ist auch sein Verdienst. Für sein prägendes Vorbild, Wissenschaft menschlich zu machen, bin ich ihm sehr dankbar. Ich bewahre ihn in Erinnerung.

Johannes Eble

Klaus Kühn was a pioneer, a titan of collagen research, and an excellent teacher and mentor. His scientific heritage and mentorship left lasting marks on connective tissue research, both in- and outside Germany. Even after his retirement, Klaus Kühn often visited his beloved Max Planck Institute of Biochemistry and always stopped by in my department to talk about the latest breakthroughs in matrix and adhesion research. His visits, discussions, support and advice will always remain in my memory.

Reinhard Fässler

Nicht nur die Wissenschaft, sondern auch viele muntere und warmherzige Treffen hat mich mit Klaus Kühn verbunden. Es sind nicht zuletzt diese Runden in anspruchsvoller Konversation und freundschaftlich, verbindlicher Atmosphäre, die uns in Erinnerung bleiben und die uns deutlich machen, welch menschlicher Verlust der fast gemeinsame Tod von Barbara und Klaus für uns bedeutet.

Peter Müller & Verena Gauss-Müller

I first got to know Klaus Kühn in 1983 when I joined Rupert Timpl´s group in the Kühn department in Martinsried. Later there were many more meetings, in particular at the famous retreats at Schloss Ringberg. Klaus was an outstanding scientist, but also a very kind and supportive mentor. I much appreciated the generosity with which he led his department. He gave us great freedom and a main priority was always the development of his younger coworkers. For this reason many of us stayed as long as ever possible. He became my role model with regard to scientific leadership. I feel deep sorrow.

Mats Paulsson

Klaus Kühn war für uns immer ein Fixpunkt als brillianter, stimulierender und immer neugieriger Wissenschaftler. Es war ein Erlebnis in seiner Abteilung, auch wenn er es einem nicht immer ganz leicht machte. Ein besonderer Mensch der Güte und Menschlichkeit ausstrahlte und dabei versuchte, die nächste Generation zu fordern und das Beste in ihnen zu fördern. In diesem Sinne erfüllt uns der Verlust mit Trauer aber auch menschlicher Dankbarkeit.

Ernst Pöschl & Ulrike Mayer

Remarkably and rewarding for us younger members in his team was his continuous support and critical but helpful guidance in research, allowing us to pursue our own ideas and thus fostering the development of a multi-facetted and productive research scene in his lab. The heritage of Klaus Kühn to the current generation of scientists should be his undeviating research commitment, his readiness for new technologies and methods, and supportive and fair attitude in dealing with young scientists and colleagues.

Klaus von der Mark

Deutsche Gesellschaft für Matrix Biologie

Read the full personal obituaries at www.matrixbiologie.de/news/

Spotlights on methods that other ISMB members may find useful

If you would like to feature in the next newsletter, please email Communication Group Coordinator Julia Etich (julia.etich@uni-koeln.de)

In Focus

An In Vivo Stable Isotope Labeling Method to Investigate Individual Matrix Protein Synthesis, Ribosomal Biogenesis, and Cellular Proliferation in Murine Articular Cartilage.
Kobak KA, Batushansky A, Borowik AK, Lopes EPB, Peelor Iii FF, Donovan EL, Kinter MT, Miller BF, Griffin TM. Function (Oxf). 2022 Feb 25;3(2):zqac008. doi: 10.1093/function/zqac008.
Corresponding author: benjamin-miller@omrf.org and tim-griffin@omrf.org
Abstract: *Targeting chondrocyte dynamics is a strategy for slowing osteoarthritis progression during aging. We describe a stable-isotope method using in vivo deuterium oxide labeling and mass spectrometry to measure protein concentration, protein half-life, cell proliferation, and ribosomal biogenesis in a single sample of murine articular cartilage. We hypothesized that a 60-d labeling period would capture age-related declines in cartilage matrix protein content, protein synthesis rates, and cellular proliferation. Knee cartilage was harvested to the subchondral bone from 25- to 90-wk-old female C57BL/6J mice treated with deuterium oxide for 15, 30, 45, and 60 d. We measured protein concentration and half-lives using targeted high resolution accurate mass spectrometry and d2ome data processing software. Deuterium enrichment was quantified in isolated DNA and RNA to measure cell proliferation and ribosomal biogenesis, respectively. Most collagen isoforms were less abundant in aged animals, with negligible collagen synthesis at either age. In contrast, age altered the concentration and half-lives of many proteoglycans and other matrix proteins, including several with greater concentration and half-lives in older mice such as proteoglycan 4, clusterin, and fibronectin-1. Cellular proteins were less abundant in older animals, consistent with reduced cellularity. Nevertheless, deuterium was maximally incorporated into 60% of DNA and RNA by 15 d of labeling in both age groups, suggesting the presence of two large pools of either rapidly (<15 d) or slowly (>60 d) proliferating cells. Our findings indicate that age-associated changes in cartilage matrix protein content and synthesis occur without detectable changes in the relative number of proliferating cells.*

Sensitive asprosin detection in clinical samples reveals serum/saliva correlation and indicates cartilage as source for serum asprosin.
Morcos YAT, Lütke S, Tenbieg A, Hanisch FG, Pryymachuk G, Piekarek N, Hoffmann T, Keller T, Janoschek R, Niehoff A, Zaucke F, Dötsch J, Hucklenbruch-Rother E, Sengle G. Sci Rep. 2022 Jan 25;12(1):1340. doi: 10.1038/s41598-022-05060-x.
Corresponding author: gsengle@uni-koeln.de
Abstract: *The C-terminal pro-fibrillin-1 propeptide asprosin is described as white adipose tissue derived hormone that stimulates rapid hepatic glucose release and activates hunger-promoting hypothalamic neurons. Numerous studies proposed correlations of asprosin levels with clinical parameters. However, the enormous variability of reported serum and plasma asprosin levels illustrates the need for sensitive and reliable detection methods in clinical samples. Here we report on newly developed biochemical methods for asprosin concentration and detection in several body fluids including serum, plasma, saliva, breast milk, and urine. Since we found that*

glycosylation impacts human asprosin detection we analyzed its glycosylation profile. Employing a new sandwich ELISA revealed that serum and saliva asprosin correlate strongly, depend on biological sex, and feeding status. To investigate the contribution of connective tissue-derived asprosin to serum levels we screened two cohorts with described cartilage turnover. Serum asprosin correlated with COMP, a marker for cartilage degradation upon running exercise and after total hip replacement surgery. This together with our finding that asprosin is produced by primary human chondrocytes and expressed in human cartilage suggests a contribution of cartilage to serum asprosin. Furthermore, we determined asprosin levels in breast milk, and urine, for the first time, and propose saliva asprosin as an accessible clinical marker for future studies.

Books & Special Issues on the Extracellular Matrix

Tenascins: Key players in tissue homeostasis and defense Frontiers Immunology Kim Midwood, Gertraud Orend, and Kyoko Imanaka-Yoshida

This issue comprises 13 review articles and 9 original articles, coauthored by over 100 researchers in the field, that elaborate on both the history and the current state of the art in the fascinating story of the tenascins in the immune context.
https://www.frontiersin.org/research-topics/13159/tenascins-key-players-in-tissue-homeostasis-and-defense

Imanaka Yoshida K*, Midwood K*, Orend G*, 2022, Editorial on special issue on Tenascins: Key Players in Tissue Homeostasis and Defense", Front Immunol, 12, 834353. doi:10.3389/fimmu.2021.834353.

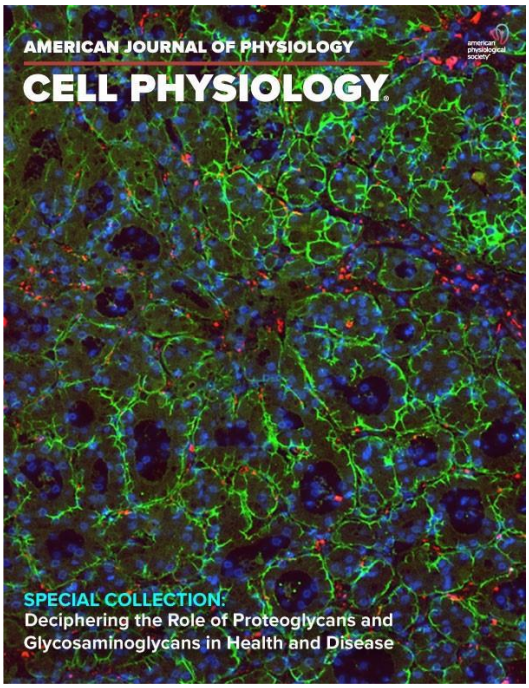
Deciphering the role of proteoglycans and glycosaminoglycans in health and disease American Journal of Physiology-Cell Physiology - Special Collection Coming June 2022 Guest Editor: Liliana Schaefer, MD, AJP-Cell Physiology Editor-in-Chief

This upcoming AJP-Cell Physiology special collection will feature a series of invited reviews discussing recent advances in proteoglycans and glycosaminoglycans. Proteoglycans are biologically active components of the extracellular matrix. They consist of a specific protein core that is post-translationally modified and covalently linked with linear glycosaminoglycans. These glycosaminoglycans consist of repeating disaccharides.

An emerging body of evidence indicates that secreted proteoglycans act as signaling molecules in addition to their canonical function in maintaining and regulating the architecture of various extracellular matrices. See the full description and learn how to submit your review proposal today: bit.ly/AJPCellProteoglycans.

@AJPCellPhys

The winning image that will serve as the cover for the proteoglycans special collection later this year in AJP-Cell Physiology (https://bit.ly/AJPCellProteoglycans).
The image was created by Ilona Kovalszky, Professor of Pathology, Semmelweis University (Budapest, Hungary).
The fluorescent immunohistochemical picture depicts a hepatocellular carcinoma, with syndecan-1 positivity on the surface of tumor cells (green) and macrophages in the tumor stroma (red). Nuclei are shown by DAPI (blue).



International travel grants

Deadline postponed to June, 1st 2022 to allow applications for Matrix Biology Europe meeting

ISMB provides international travel grants (on average 500 € for young scientists (graduate students or postdocs up to 5 years after Ph.D.) to allow them to attend major meetings in matrix biology anywhere in the world. While priority will be given to meetings directly supported by ISMB (including Matrix Biology Europe, the American Society for Matrix Biology and the Pan Pacific Connective Tissue Societies Symposium), applications are accepted for any meeting, provided that the scope of the meeting agrees with the aims of the Society.

In the current context of the COVID-19 pandemic, applications for on-line, hybrid and in-person meetings will all be considered.

To apply for a travel grant, please send your application to the ISMB secretary, in the form of a single pdf file containing: (1) a letter giving information about the meeting, the amount requested and a detailed justification for support, (2) the abstract of your poster/short talk, (3) your curriculum vitae and list of publications.

Please apply several months in advance of the meeting, before one of the following deadlines: January 1, April 1, July 1, October 1.

Candidates should be members of the ISMB (see membership page for details), and a graduate student or postdoc. up to 5 years after Ph.D., (with extensions for maternity leave, military service, etc). Grants are for international travel only and will be awarded on the basis of scientific excellence and relevance to matrix biology. Successful candidates will be notified no more than one month after each deadline. Following the meeting, awardees will be expected to send to the ISMB a certificate of attendance as well as a short report (to appear on the ISMB web site with some selected for the ISMB newsletter) in the form of a personal perspective on their experience at the meeting. All reimbursement claims and reports must be received within 3 months after the end of the conference.

Two free registrations to ECM 2022 meeting (Copenhagen, July 23rd-26th, 2022) offered by the organizers to the ISMB

Chrysostomi Gialeli, Associate Researcher, University of Lund (Sweden) and Annalena Dittmann, PhD student, University of Oulu (Finlznd) were selected by the ISMB executive committee for a free registration to ECM 2022.

Recent publications

An adapted passive model of anti-MPO dependent crescentic glomerulonephritis reveals matrix dysregulation and is amenable to modulation by CXCR4 inhibition.
Abou Faycal C, Oszwald A, Feilen T, Contreras MJC, Schilling O, Loustau T, Steinbach F, Schachner H, Langer B, Heeringa P, Rees AJ, Orend G, Kain R. Matrix Biol. 2022 Jan 12:S0945-053X(22)00001-4. doi: 10.1016/j.matbio.2022.01.001.
Corresponding authors: gertraud.orend@inserm.fr and renate.kain@meduniwein.ac.at
Abstract: *Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are severe inflammatory disorders that often involve focal necrotizing glomerulonephritis (FNGN) and consequent glomerular scarring, interstitial fibrosis, and chronic kidney disease. Robust murine models of scarring in FNGN that may help to further our understanding of deleterious processes are still lacking. Here, we present a murine model of severe FNGN based on combined administration of antibodies against the glomerular basement membrane (GBM) and myeloperoxidase (MPO), and bacterial lipopolysaccharides (LPS), that recapitulates acute injury and was adapted to investigate subsequent glomerular and interstitial scarring. Hematuria without involvement of other organs occurs consistently and rapidly, glomerular necrosis and crescent formation are evident at 12 days, and*

consequent glomerular and interstitial scarring at 29 days after initial treatment. Using mass-spectrometric proteome analysis, we provide a detailed overview of matrisomal and cellular changes in our model. We observed increased expression of the matrisome including collagens, fibronectin, tenascin-C, in accordance with human AAV as deduced from analysis of gene expression microarrays and tissue staining. Moreover, we observed tissue infiltration by neutrophils, macrophages, T cells and myofibroblasts upon injury. Experimental inhibition of CXCR4 using AMD3100 led to a sustained histological presence of fibrin extravasate, reduced chemokine expression and leukocyte activation, but did not markedly affect ECM composition. Altogether, we demonstrate an adapted FNGN model that enables the study of matrisomal changes both in disease and upon intervention, as exemplified via CXCR4 inhibition.

Vertebrate lonesome kinase modulates the hepatocyte secretome to prevent perivascular liver fibrosis and inflammation.

Pantasis S, Friemel J, Brütsch SM, Hu Z, Krautbauer S, Liebisch G, Dengjel J, Weber A, Werner S, Bordoli MR.
J Cell Sci. 2022 Mar 16:jcs.259243. doi: 10.1242/jcs.259243. Online ahead of print. PMID: 35293576
Corresponding author: sabine.werner@biol.ethz.ch and mattia.bordoli@novartis.com
Abstract: *Vertebrate lonesome kinase (VLK) is the only known extracellular tyrosine kinase, but its physiological functions are largely unknown. We show that VLK is highly expressed in hepatocytes of neonatal mice, but down-regulated during adulthood. To determine the role of VLK in liver homeostasis and regeneration we generated mice with a hepatocyte-specific knockout of the VLK gene (Pkdcc). Cultured progenitor cells established from primary hepatocytes of Pkdcc knockout mice produced a secretome, which promoted their own proliferation in 3D spheroids and proliferation of cultured fibroblasts. In vivo, Pkdcc knockout mice developed liver steatosis with signs of inflammation and perivascular fibrosis upon aging, combined with expansion of liver progenitor cells. In response to chronic CCl4-induced liver injury, the pattern of deposited collagen was significantly altered in these mice. The liver injury marker alpha-fetoprotein was increased in the secretome of VLK-deficient cultured progenitor cells and in tissue of aged or CCl4-treated knockout mice. These results support a key role for VLK and extracellular protein phosphorylation in liver homeostasis and repair through paracrine control of liver cell function and regulation of appropriate collagen deposition.*

Modulating tenascin-C functions by targeting the MAtrix REgulating MOtif, "MAREMO"

Loustau T*, Abou-Faycal C*, Erne W*, Abel zur Wiesch P*, Ksouri A, Imhof T, Mörgelin M, Li C, Mathieu M, Salomé N, Crémel G, Dhaouadi S, Bouhaouala-Zahar B, Koch M, Orend G,. 2022. Matrix Biol, S0945-053X(22)00025-7. doi: 10.1016/j.matbio.2022.02.007. PMID: 35227929
Corresponding author: gertraud.orend@inserm.fr
Abstract: *The extracellular matrix molecule Tenascin-C (TNC) promotes cancer and chronic inflammation by multiple mechanisms. Recently, TNC was shown to promote an immune suppressive tumor microenvironment (TME) through binding soluble chemoattracting factors, thus retaining leukocytes in the stroma. TNC also binds to fibronectin (FN) and other molecules, raising the question of a potential common TNC binding mechanism. By sequence comparison of two TNC-interacting domains in FN, the fifth (FN5) and thirteenth (FN13) fibronectin type III domains we identified a MAtrix REgulating MOtif "MAREMO" or M-motif that is highly conserved amongst vertebrates. By sequence analysis, structural modeling and functional analysis we found also putative M-motifs in TNC itself. We showed by negative staining electron microscopic imaging that the M-motif in FN mediates interactions with FN as well as with TNC. We generated two M-motif mimetic peptides P5 and P13 resembling the M-motif in FN5 and FN13, respectively. By using structural information we modelled binding of these M-motif mimetics revealing a putative MAREMO binding site MBS in FN5 and TN3, respectively overlapping with the M-*

motif. We further demonstrated that the M-motif mimetic peptides blocked several functions of TNC, such as binding of TNC to FN, cell rounding on a mixed FN/TNC substratum, FN matrix expression and subsequent assembly, TNC-induced signaling and gene expression, TNC chemokine binding and dendritic cell retention, thus providing novel opportunities to inhibit TNC actions. Our results suggest that targeting the MAREMO/MBS interaction could be exploited for reducing inflammation and matrix functions in cancer and fibrosis.

Latent TGFβ complexes are transglutaminase cross-linked to fibrillin to facilitate TGFβ activation.
Lockhart-Cairns MP, Cain SA, Dajani R, Steer R, Thomson J, Alanazi YF, Kielty CM, Baldock C. Matrix Biol. 2022 107:24-39. doi:10.1016/j.matbio.2022.01.005.
Corresponding author: clair.baldock@manchester.ac.uk
Abstract: *TGFβ superfamily members are potent growth factors in the extracellular matrix with essential roles in all aspects of cellular behaviour. Latent TGFβ binding proteins (LTBPs) are co-expressed with TGFβ, essential for correct folding and secretion of the growth factor, to form large latent complexes. These large latent complexes bind extracellular proteins such as fibrillin for sequestration of TGFβ in the matrix, essential for normal tissue function, and dysregulated TGFβ signalling is a hallmark of many fibrillinopathies. Transglutaminase-2 (TG2) cross-linking of LTBPs is known to play a role in TGFβ activation but the underlying molecular mechanisms are not resolved. Here we show that fibrillin is a matrix substrate for TG2 and that TG2 cross-linked complexes can be formed between fibrillin and LTBP-1 and -3, and their latent TGFβ complexes. The structure of the fibrillin-LTBP1 complex shows that the two elongated proteins interact in a perpendicular arrangement which would allow them to form distal interactions between the matrix and the cell surface. Formation of the cross-link with fibrillin does not change the interaction between latent TGFβ and integrin αVβ6 but does increase TGFβ activation in cell-based assays. The activating effect may be due to direction of the latent complexes to the cell surface by fibrillin, as competition with heparan sulphate can ameliorate the activating effect. Together, these data support that TGFβ activation can be enhanced by covalent tethering of LTBPs to the matrix via fibrillin.*

The natural antisense transcript HAS2-AS1 regulates breast cancer cells aggressiveness independently from hyaluronan metabolism.
Parnigoni A, Caon I, Teo WX, Hua SH, Moretto P, Bartolini B, Viola M, Karousou E, Yip GW, Götte M, Heldin P, Passi A, Vigetti D. Matrix Biol. 2022 Apr 5;S0945-053X(22)00051-8. doi: 10.1016/j.matbio.2022.03.009.
Corresponding author: Davide.vigetti@uninsubria.it
Abstract: *Hyaluronan (HA) is a ubiquitous extracellular matrix component playing a crucial role in the regulation of cell behaviors, including cancer. Aggressive breast cancer cells tend to proliferate, migrate and metastatize. Notably, triple-negative breast cancer cells lacking the expression of estrogen receptor (ER) as well as progesterone receptor and HER2 are more aggressive than ER-positive ones. As currently no targeted therapy is available for triple-negative breast cancer, the identification of novel therapeutic targets has a high clinical priority. In ER-negative cells, tumoral behavior can be reduced by inhibiting HA synthesis or silencing the enzymes involved in its metabolism, such as HA synthase 2 (HAS2). HAS2-AS1 is a long non-coding RNA belonging to the natural antisense transcript family which is known to favor HAS2 gene expression and HA synthesis, thus bolstering malignant progression in brain, ovary, and lung tumors. As the role of HAS2-AS1 has not yet been investigated in breast cancer, in this work we report that ER-positive breast cancers had lower HAS2-AS1 expression compared to ER-negative tumors. Moreover, the survival of patients with ER-negative tumors was higher when the expression of HAS2-AS1 was elevated. Experiments with ER-negative cell lines as MDA-MB-231 and Hs 578T revealed that the overexpression of either the full-length HAS2-AS1 or its exon 2 long or short isoforms alone, strongly reduced cell viability, migration, and invasion, whereas HAS2-AS1 silencing increased cell aggressiveness. Unexpectedly, in*

these ER-negative cell lines, HAS2-AS1 is involved neither in the regulation of HAS2 nor in HA deposition. Finally, transcriptome analysis revealed that HAS2-AS1 modulation affected several pathways, including apoptosis, proliferation, motility, adhesion, epithelial to mesenchymal transition, and signaling, describing this long non-coding RNA as an important regulator of breast cancer cells aggressiveness.

Lack of the myotendinous junction marker col22a1 results in posture and locomotion disabilities in zebrafish. Malbouyres M, Guiraud A, Lefrançois C, Salamito M, Nauroy P, Bernard L, Sohm F, Allard B, Ruggiero F. Matrix Biol. 2022 Mar 9:S0945-053X(22)00034-8. doi: 10.1016/j.matbio.2022.03.002. Online ahead of print.
Corresponding author: florence.ruggiero@ens-lyon.fr
Abstract: *The myotendinous junction (MTJ) is essential for the integrity of the musculoskeletal unit. Here, we show that gene ablation of the MTJ marker col22a1 in zebrafish results in MTJ dysfunction but with variable degrees of expression and distinct phenotypic classes. While most individuals reach adulthood with no overt muscle phenotype (class 1), a subset of the progeny displays severe movement impairment and die before metamorphosis (class 2). Yet all mutants display muscle weakness due to ineffective muscle force transmission that is ultimately detrimental for class-specific locomotion-related functions. Movement impairment at the critical stage of swimming postural learning causes class 2 larval death by compromising food intake. In class 1 adults, intensive exercise is required to uncover a decline in muscle performance, accompanied by higher energy demand and mitochondrial adaptation. This study underscores COL22A1 as a candidate gene for myopathies associated with dysfunctional force transmission and anticipates a phenotypically heterogeneous disease.*

Biglycan interacts with type I insulin-like receptor (IGF-IR) signaling pathway to regulate osteosarcoma progression and response to chemotherapy. Giatagana E-M., Berdiaki A., Gaardløs M., Samsonov S.A., Tzanakakis G.N., Nikitovic D. Cancers. 2022. Vol 14: 1196. https://doi.org/10.3390/cancers14051196
Corresponding author: nikitovic@uoc.gr
Abstract: *Osteosarcoma (OS) is a mesenchymally derived, aggressive bone cancer. OS cells produce an aberrant nonmineralized or partly mineralized extracellular matrix (ECM) whose components participate in signaling pathways connected to specific pathogenic phenotypes of this bone cancer. The expression of biglycan (BGN), a secreted small leucine-rich proteoglycan (SLRP), is correlated to aggressive OS phenotype and resistance to chemotherapy. A constitutive signaling of IGF-IR signaling input in sarcoma progression has been established. Here, we show that biglycan activates the IGF-IR signaling pathway to promote MG63 biglycan-secreting OS cell growth by forming a complex with the receptor. Computational models of IGF-IR and biglycan docking suggest that biglycan binds IGF-IR dimer via its concave surface. Our binding free energy calculations indicate the formation of a stable complex. Biglycan binding results in prolonged IGF-IR activation leading to protracted IGF-IR-dependent cell growth response of the poorly-differentiated MG63 cells. Moreover, biglycan facilitates the internalization ($p \leq 0.01$, $p \leq 0.001$) and sumoylation-enhanced nuclear translocation of IGF-IR ($p \leq 0.05$) and its DNA binding in MG63 cells ($p \leq 0.001$). The tyrosine kinase activity of the receptor mediates this mechanism. Furthermore, biglycan downregulates the expression of the tumor-suppressor gene, PTEN ($p \leq 0.01$), and increases the expression of endothelial-mesenchymal transition (EMT) and aggressiveness markers vimentin ($p \leq 0.01$) and fibronectin ($p \leq 0.01$) in MG63 cells. Interestingly, this mechanism is not valid in moderately and well-differentiated, biglycan non-expressing U-2OS and Saos-2 OS cells. Furthermore, biglycan exhibits protective effects against the chemotherapeutic drug, doxorubicin, in MG63 OS cells ($p \leq 0.01$). In conclusion, these data indicate a potential direct and adjunct therapeutical role of biglycan in osteosarcoma.*

In silico and in vitro mapping of specificity patterns of glycosaminoglycans towards cysteine cathepsins B, L, K, S and V. Bojarski K.K., Sage J., Lalmanach G., Lecaille F., Samsonov S.A. J Mol Graph Mod. 2022. Vol. 113: 108153 https://doi.org/10.1016/j.jmgm.2022.108153

Corresponding author: sergey.samsonov@ug.edu.pl

Abstract: *Human cysteine cathepsins are lysosomal proteases, which are involved in different biological processes. Their enzymatic activity can be regulated by glycosaminoglycans (GAGs): long linear periodic negatively charged polysaccharides, which dimeric building blocks consist of uronic acid and hexosamine monosaccharide units. In this study, molecular docking simulations of chondroitin 4-sulfate, chondroitin 6-sulfate, heparin, heparan sulfate, dermatan sulfate and hyaluronic acid of various chain lengths were performed with cathepsins B, L, K, S and V and followed by molecular dynamics-based refinement and binding free energy analysis. We concluded that electrostatics might be a driving force for cathepsin-GAG interactions; indeed as in most of characterised systems, the increase of GAG chain length consequently leads to a more pronounced effect on the strength of cathepsin-GAG interactions. Results also suggest that binding of GAGs at different regions on cathepsins surface affect differently their enzymatic activity and could is dependent on cathepsin and GAG type. Present data contribute to systematic description of cathepsin-GAG interactions, which is helpful in understanding the subtle molecular mechanisms of protease regulation behind their biological functions.*

Modulation of the expression and activity of cathepsin S in reconstructed human skin by neohesperidin dihydrochalcone. Sage J., Renault J., Domain R., Bojarski K.K., Chazeirat T., Saidi A., Leblanc E., Nizard C., Samsonov S.A., Kurfurst R., Lalmanach G., Lecaille F. Matrix Biology. 2022. Vol. 107: 97-112. https://doi.org/10.1016/j.matbio.2022.02.003

Corresponding author: fabien.lecaille@univ-tours.fr

Abstract: *Dysregulation of cathepsin S (Cat S), a cysteine protease involved in extracellular-matrix and basement membrane (BM) degradation, is a concomitant feature of several inflammatory skin diseases. Therefore, Cat S has been suggested as a potential therapeutic target. Flavonoids, which were identified as regulatory molecules of various proteolytic enzymes, exert beneficial effects on skin epidermis. Herein, thirteen flavonoid compounds were screened in vitro and in silico and neohesperidin dihydrochalcone (NHDC) was identified as a potent, competitive, and selective inhibitor (Ki=8±1 µM) of Cat S. Furthermore, Cat S-dependent hydrolysis of nidogen-1, a keystone protein of BM architecture, as well elastin, collagens I and IV was impaired by NHDC, while both expression and activity of Cat S were significantly reduced in NHDC-treated human keratinocytes. Moreover, a reconstructed human skin model showed a significant decrease of both mRNA and protein levels of Cat S after NHDC treatment. Conversely, the expression of nidogen-1 was significantly increased. NHDC raised IL-10 expression, an anti-inflammatory cytokine, and mediated STAT3 signaling pathway, which in turn dampened Cat S expression. Our findings support that NHDC may represent a valuable scaffold for structural improvement and development of Cat S inhibitors to preserve the matrix integrity and favor skin homeostasis during inflammatory events.*

PDIA3/ERp57 promotes a matrix-rich secretome that stimulates fibroblast adhesion through CCN2. Hellewell AL, Heesom KJ, Jepson MA, Adams JC. AJP-Cell Physiology, 28 MAR 2022 https://doi.org/10.1152/ajpcell.00258.2021

Corresponding author: jo.adams@bristol.ac.uk

Abstract: *The matricellular glycoprotein thrombospondin-1 (TSP1) has complex roles in the extracellular matrix (ECM) and at cell surfaces, but relatively little is known about its intracellular associations prior to secretion. To search for novel intracellular interactions of TSP1 in situ, we carried out a biotin ligase-based TSP1 interactome screen and identified protein disulfide isomerase A3 (PDIA3/ERp57) as a novel candidate binding protein. In*

validation, TSP1 and PDIA3 were established to bind in vitro and to colocalize in the endoplasmic reticulum of human dermal fibroblasts (HDF). Loss of PDIA3 function, either by pharmacological inhibition in HDF or in Pdia3−/−mouse embryo fibroblasts (Pdia3−/− MEFs), led to alterations in the composition of cell-derived extracellular matrix, involving changed abundance of fibronectin and TSP1, was correlated with reduced cell spreading, altered organization of F-actin, and reduced focal adhesions. These cellular phenotypes of Pdia3−/− MEFs were normalized by exposure to conditioned medium (WTCM) or extracellular matrix (WTECM) from wild-type (WT)-MEFs. Rescue depended on PDIA3 activity in WT-MEFs and was not prevented by immunodepletion of fibronectin. Heparin-binding proteins in WTCM were found to be necessary for rescue. Comparative quantitative tandem-mass-tag proteomics and functional assays on the heparin-binding secretomes of WT-MEFs and Pdia3−/− MEFs identified multiple ECM and growth factor proteins to be downregulated in the CM of Pdia3−/− MEFs. Of these, cell communication network 2 (CCN2) was identified to be necessary for the adhesion-promoting activity of WTCM on Pdia3−/− MEFs and to bind TSP1. Thus, PDIA3 coordinates fibroblast production of an ECM-rich, proadhesive microenvironment, with implications for PDIA3 as a translational target.

CDK1-cyclin-B1-induced kindlin degradation drives focal adhesion disassembly at mitotic entry.
Chen NP, Aretz J, Fässler R. Nat Cell Biol. 2022 Apr 25. doi: 10.1038/s41556-022-00886-z.
Corresponding author: nchen@biochem.mpg.de and faessler@biochem.mpg.de
Abstract: *The disassembly of integrin-containing focal adhesions (FAs) at mitotic entry is essential for cell rounding, mitotic retraction fibre formation, bipolar spindle positioning and chromosome segregation. The mechanism that drives FA disassembly at mitotic entry is unknown. Here, we show that the CDK1-cyclin B1 complex phosphorylates the integrin activator kindlin, which results in the recruitment of the cullin 9-FBXL10 ubiquitin ligase complex that mediates kindlin ubiquitination and degradation. This molecular pathway is essential for FA disassembly and cell rounding, as phospho-inhibitory mutations of the CDK1 motif prevent kindlin degradation, FA disassembly and mitotic cell rounding. Conversely, phospho-mimetic mutations promote kindlin degradation in interphase, accelerate mitotic cell rounding and impair mitotic retraction fibre formation. Despite the opposing effects on kindlin stability, both types of mutations cause severe mitotic spindle defects, apoptosis and aneuploidy. Thus, the exquisite regulation of kindlin levels at mitotic entry is essential for cells to progress accurately through mitosis.*

Relationship between different serum cartilage biomarkers in the acute response to running and jumping in healthy male individuals.
Dreiner M, Munk T, Zaucke F, Liphardt AM, Niehoff A. Sci Rep. 2022 Apr 19;12(1):6434. doi: 10.1038/s41598-022-10310-z.
Corresponding author: niehoff@dshs-koeln.de
Abstract: *The effect of physical activity on serum cartilage biomarkers is largely unknown. The purpose of the study was to systematically analyze the acute effect of two frequently used exercise interventions (running and jumping) on the correlation of seven serum biomarkers that reflect cartilage extracellular matrix metabolism. Fifteen healthy male volunteers (26 ± 4 years, 181 ± 4 cm, 77 ± 6 kg) participated in the repeated measurement study. In session 1, the participants accomplished 15 × 15 series of reactive jumps within 30 min. In session 2, they ran on a treadmill (2.2 m/s) for 30 min. Before and after both exercise protocols, four blood samples were drawn separated by 30 min intervals. Serum concentrations of seven biomarkers were determined: COMP, MMP-3, MMP-9, YKL-40, resistin, Coll2-1 and Coll2-1 NO2. All biomarkers demonstrated an acute response to mechanical loading. Both the COMP and MMP-3 responses were significantly ($p = 0.040$ and $p = 0.007$) different between*

running and jumping (COMP: jumping + 31%, running + 37%; MMP-3: jumping + 14%, running + 78%). Resistin increased only significantly ($p < 0.001$) after running, and Coll2-1 NO2 increased significantly ($p = 0.001$) only after jumping. Significant correlations between the biomarkers were detected. The relationships between individual serum biomarker concentrations may reflect the complex interactions between degrading enzymes and their substrates in ECM homeostasis.

Differential Impact of Membrane-Bound and Soluble Forms of the Prognostic Marker Syndecan-1 on the Invasiveness, Migration, Apoptosis, and Proliferation of Cervical Cancer Cells.

Hilgers K, Ibrahim SA, Kiesel L, Greve B, Espinoza-Sánchez NA, Götte M. Front Oncol. 2022 Jan 27;12:803899. doi: 10.3389/fonc.2022.803899.

Corresponding author: mgotte@uni-muenster.de

Abstract: *Cervical cancer ranks fourth among the most commonly diagnosed malignant tumors in women worldwide. Previously published evidence suggested a possible connection between the expression of the membrane-bound heparan sulfate proteoglycan syndecan-1 (Sdc-1) and the development of cervical carcinoma. Sdc-1 serves as a matrix receptor and coreceptor for receptor tyrosine kinases and additional signaling pathways. It influences cell proliferation, adhesion, and migration and is seen as a modulator of the tumor microenvironment. Following proteolytic cleavage of its extracellular domain in a process called shedding, Sdc-1 can act as a paracrine effector. The loss of Sdc-1 expression is associated with low differentiation of cervical carcinoma and with an increased rate of lymph node metastases. Here, we analyzed the clinical impact of Sdc-1 expression by analysis of public gene expression datasets and studied the effect of an overexpression of Sdc-1 and its membrane-bound and soluble forms on the malignant properties of the human cervical carcinoma cell line HeLa through functional analysis. For this purpose, the HeLa cells were stably transfected with the control plasmid pcDNA3.1 and three different Sdc-1-DNA constructs,encoding wild-type, permanently membrane-bound, and constitutively soluble Sdc-1. In clinical specimens, Sdc-1 mRNA was more highly expressed in local tumor tissues than in normal and metastatic cervical cancer tissues. Moreover, high Sdc-1 expression correlated with a poor prognosis in Kaplan-Meier survival analysis, suggesting the important role of Sdc-1 in the progression of this type of cancer. In vitro, we found that the soluble, as well as the permanently membrane-bound forms of Sdc-1 modulated the proliferation and the cell cycle, while membrane-bound Sdc1 regulated HeLa cell apoptosis. The overexpression of Sdc-1 and its soluble form increased invasiveness. In vitro scratch/wound healing assay, showed reduced Sdc-1-dependent cell motility which was linked to the Rho-GTPase signaling pathway. In conclusion, in cervical cancer Sdc-1 modulates pathogenetically relevant processes, which depend on the membrane-association of Sdc-1.*

NFκB inhibition to lift the mechano-competence of mesenchymal stromal cell-derived neocartilage toward articular chondrocyte levels.

Lückgen J, Raqué E, Reiner T, Diederichs S, Richter W. Stem Cell Res Ther. 2022 Apr 27;13(1):168. doi: 10.1186/s13287-022-02843-x.

Corresponding author: wiltrud.richter@med.uni-heidelberg.de

Abstract: *Background: Fully functional regeneration of skeletal defects by multipotent progenitor cells requires that differentiating cells gain the specific mechano-competence needed in the target tissue. Using cartilage neogenesis as an example, we asked whether proper phenotypic differentiation of mesenchymal stromal cells (MSC) into chondrocytes in vitro will install the adequate biological mechano-competence of native articular chondrocytes (AC). Methods: The mechano-competence of human MSC- and AC-derived neocartilage was compared during differentiation for up to 35 days. The neocartilage layer was subjected to physiologic dynamic loading in a custom-designed bioreactor and assayed for mechano-sensitive gene and pathway activation,*

extracellular matrix (ECM) synthesis by radiolabel incorporation, nitric oxide (NO) and prostaglandin E2 (PGE2) production. Input from different pathways was tested by application of agonists or antagonists. Results: MSC and AC formed neocartilage of similar proteoglycan content with a hardness close to native tissue. Mechano-stimulation on day 21 and 35 induced a similar upregulation of mechano-response genes, ERK phosphorylation, NO production and PGE2 release in both groups, indicating an overall similar transduction of external mechanical signals. However, while AC maintained or enhanced proteoglycan synthesis after loading dependent on tissue maturity, ECM synthesis was always significantly disturbed by loading in MSC-derived neocartilage. This was accompanied by significantly higher COX2 and BMP2 background expression, > 100-fold higher PGE2 production and a weaker SOX9 stimulation in response to loading in MSC-derived neocartilage. Anabolic BMP-pathway activity was not rate limiting for ECM synthesis after loading in both groups. However, NFκB activation mimicked the negative loading effects and enhanced PGE2 production while inhibition of catabolic NFκB signaling rescued the load-induced negative effects on ECM synthesis in MSC-derived neocartilage. Conclusions: MSC-derived chondrocytes showed a higher vulnerability to be disturbed by loading despite proper differentiation and did not acquire an AC-like mechano-competence to cope with the mechanical stress of a physiologic loading protocol. Managing catabolic NFκB influences was one important adaptation to install a mechano-resistance closer to AC-derived neocartilage. This new knowledge asks for a more functional adaptation of MSC chondrogenesis, novel pharmacologic co-treatment strategies for MSC-based clinical cartilage repair strategies and may aid a more rational design of physical rehabilitation therapy after AC- versus MSC-based surgical cartilage intervention.

ATP allosterically stabilizes integrin-linked kinase for efficient force generation.
Martin IM, Nava MM, Wickström SA, Gräter F. Proc Natl Acad Sci U S A. 2022 Mar 15;119(11):e2106098119. doi: 10.1073/pnas.2106098119.
Corresponding author: sara.wickstrom@helsinki.fi and frauke.graeter@h.its.org
Abstract: *The pseudokinase integrin-linked kinase (ILK) is a central component of focal adhesions, cytoplasmic multiprotein complexes that integrate and transduce biochemical and mechanical signals from the extracellular environment into the cell and vice versa. However, the precise molecular functions, particularly the mechanosensory properties of ILK and the significance of retained adenosine triphosphate (ATP) binding, are still unclear. Combining molecular-dynamics simulations with cell biology, we establish a role for ATP binding to pseudokinases. We find that ATP promotes the structural stability of ILK, allosterically influences the interaction between ILK and its binding partner parvin at adhesions, and enhances the mechanoresistance of this complex. On the cellular level, ATP binding facilitates efficient traction force buildup, focal adhesion stabilization, and efficient cell migration.*

LTBP1 promotes fibrillin incorporation into the extracellular matrix.
Przyklenk M, Georgieva VS, Metzen F, Mostert S, Kobbe B, Callewaert B, Sengle G, Brachvogel B, Mecham RP, Paulsson M, Wagener R, Koch M, Schiavinato A. Matrix Biol. 2022 Apr 19:S0945-053X(22)00056-7. doi: 10.1016/j.matbio.2022.04.004.
Corresponding author: aschiav1@uni-koeln.de
Abstract: *LTBP1 is a large extracellular matrix protein and an associated ligand of fibrillin-microfibrils. Knowledge of LTBP1 functions is largely limited to its role in targeting and sequestering TGFβ growth factors within the extracellular matrix, thereby regulating their bioavailability. However, the recent description of a wide spectrum of phenotypes in multiple tissues in patients harboring LTBP1 pathogenic variants suggests a multifaceted role of the protein in the homeostasis of connective tissues. To better understand the human pathology caused by LTBP1 deficiency it is important to investigate its functional role in extracellular matrix formation. In this study, we show*

that LTBP1 coordinates the incorporation of fibrillin-1 and -2 into the extracellular matrix in vitro. We also demonstrate that this function is differentially exerted by the two isoforms, the short and long forms of LTBP1. Thereby our findings uncover a novel TGFβ-independent LTBP1 function potentially contributing to the development of connective tissue disorders.

Matritecture: Mapping the extracellular matrix architecture during health and disease.
Reuten R, Mayorca-Guiliani AE, Erler JT. Matrix Biol Plus. 2022 Feb 3;14:100102. doi: 10.1016/j.mbplus.2022.100102.
Corresponding author: raphael.reuten@pharmakol.uni-freiburg.de and alejandro.mayorca@bric.ku.dk and janine.erler@bric.ku.dk
Abstract: *All cells in multicellular organisms are housed in the extracellular matrix (ECM), an acellular edifice built up by more than a thousand proteins and glycans. Cells engage in a reciprocal relationship with the ECM; they build, inhabit, maintain, and remodel the ECM, while, in turn, the ECM regulates their behavior. The homeostatic balance of cell-ECM interactions can be lost, due to ageing, irritants or diseases, which results in aberrant cell behavior. The ECM can suppress or promote disease progression, depending on the information relayed to cells. Instructions come in the form of biochemical (e.g., composition), biophysical (e.g., stiffness), and topographical (e.g., structure) cues. While advances have been made in many areas, we only have a very limited grasp of ECM topography. A detailed atlas deciphering the spatiotemporal arrangement of all ECM proteins is lacking. We feel that such an extracellular matrix architecture (matritecture) atlas should be a priority goal for ECM research. In this commentary, we will discuss the need to resolve the spatiotemporal matritecture to identify potential disease triggers and therapeutic targets and present strategies to address this goal. Such a detailed matritecture atlas will not only identify disease-specific ECM structures but may also guide future strategies to restructure disease-related ECM patterns reverting to a normal pattern.*

Pathophysiology of systemic sclerosis (scleroderma).
Rosendahl AH, Schönborn K, Krieg T. Kaohsiung J Med Sci. 2022 Mar;38(3):187-195. doi: 10.1002/kjm2.12505.
Corresponding author: thomas.krieg@uni-koeln.de
Abstract: *Systemic sclerosis (scleroderma) is an autoimmune-triggered chronic fibrosing disease that affects the skin and many other organs. Its pathophysiology is complex and involves an early endothelial damage, an inflammatory infiltrate and a resulting fibrotic reaction. Based on a predisposing genetic background, an altered balance of the acquired and the innate immune system leads to the release of many cytokines and chemokines as well as autoantibodies, which induce the activation of fibroblasts with the formation of myofibroblasts and the deposition of a stiff and rigid connective tissue. A curative treatment is still not available but remarkable progress has been made in the management of organ complications. In addition, several breakthroughs in the pathophysiology have led to new therapeutic concepts. Based on these, many new compounds have been developed during the last years, which target these different pathways and offer specific therapeutic approaches.*

β2-Adrenoceptor Deficiency Results in Increased Calcified Cartilage Thickness and Subchondral Bone Remodeling in Murine Experimental Osteoarthritis.
Rösch G, Muschter D, Taheri S, El Bagdadi K, Dorn C, Meurer A, Zaucke F, Schilling AF, Grässel S, Straub RH, Jenei-Lanzl Z. Front Immunol. 2022 Jan 13;12:801505. doi: 10.3389/fimmu.2021.801505.
Corresponding author: zsuzsa.jenei-lanzl@kgu.de
Abstract: *Purpose: Recent studies demonstrated a contribution of adrenoceptors (ARs) to osteoarthritis (OA) pathogenesis. Several AR subtypes are expressed in joint tissues and the β2-AR subtype seems to play a major role*

during OA progression. However, the importance of β2-AR has not yet been investigated in knee OA. Therefore, we examined the development of knee OA in β2-AR-deficient (Adrb2-/-) mice after surgical OA induction. Methods: OA was induced by destabilization of the medial meniscus (DMM) in male wildtype (WT) and Adrb2-/- mice. Cartilage degeneration and synovial inflammation were evaluated by histological scoring. Subchondral bone remodeling was analyzed using micro-CT. Osteoblast (alkaline phosphatase - ALP) and osteoclast (cathepsin K - CatK) activity were analyzed by immunostainings. To evaluate β2-AR deficiency-associated effects, body weight, sympathetic tone (splenic norepinephrine (NE) via HPLC) and serum leptin levels (ELISA) were determined. Expression of the second major AR, the α2-AR, was analyzed in joint tissues by immunostaining. Results: WT and Adrb2-/- DMM mice developed comparable changes in cartilage degeneration and synovial inflammation. Adrb2-/- DMM mice displayed elevated calcified cartilage and subchondral bone plate thickness as well as increased epiphyseal BV/TV compared to WTs, while there were no significant differences in Sham animals. In the subchondral bone of Adrb2-/- mice, osteoblasts activity increased and osteoclast activity deceased. Adrb2-/- mice had significantly higher body weight and fat mass compared to WT mice. Serum leptin levels increased in Adrb2-/- DMM compared to WT DMM without any difference between the respective Shams. There was no difference in the development of meniscal ossicles and osteophytes or in the subarticular trabecular microstructure between Adrb2-/- and WT DMM as well as Adrb2-/- and WT Sham mice. Number of α2-AR-positive cells was lower in Adrb2-/- than in WT mice in all analyzed tissues and decreased in both Adrb2-/- and WT over time. Conclusion: We propose that the increased bone mass in Adrb2-/- DMM mice was not only due to β2-AR deficiency but to a synergistic effect of OA and elevated leptin concentrations. Taken together, β2-AR plays a major role in OA-related subchondral bone remodeling and is thus an attractive target for the exploration of novel therapeutic avenues.

Impact of Musashi-1 and Musashi-2 Double Knockdown on Notch Signaling and the Pathogenesis of Endometriosis.

Strauß T, Greve B, Gabriel M, Achmad N, Schwan D, Espinoza-Sanchez NA, Laganà AS, Kiesel L, Poutanen M, Götte M, Schäfer SD. Int J Mol Sci. 2022 Mar 5;23(5):2851. doi: 10.3390/ijms23052851.

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Abstract: *The stem cell marker and RNA-binding protein Musashi-1 is overexpressed in endometriosis. Musashi-1-siRNA knockdown in Ishikawa cells altered the expression of stem cell related genes, such as OCT-4. To investigate the role of both human Musashi homologues (MSI-1 and MSI-2) in the pathogenesis of endometriosis, immortalized endometriotic 12-Z cells and primary endometriotic stroma cells were treated with Musashi-1- and Musashi-2-siRNA. Subsequently, the impact on cell proliferation, cell apoptosis, cell necrosis, spheroid formation, stem cell phenotype and the Notch signaling pathway was studied in vitro. Using the ENDOMET Turku Endometriosis database, the gene expression of stem cell markers and Notch signaling pathway constituents were analyzed according to localization of the endometriosis lesions. The database analysis demonstrated that expression of Musashi and Notch pathway-related genes are dysregulated in patients with endometriosis. Musashi-1/2-double-knockdown increased apoptosis and necrosis and reduced stem cell gene expression, cell proliferation, and the formation of spheroids. Musashi silencing increased the expression of the anti-proliferation mediator p21. Our findings suggest the therapeutic potential of targeting the Musashi-Notch axis. We conclude that the Musashi genes have an impact on Notch signaling and the pathogenesis of endometriosis through the downregulation of proliferation, stemness characteristics and the upregulation of apoptosis, necrosis and of the cell cycle regulator p21.*

Proteolysis of fibrillin-2 microfibrils is essential for normal skeletal development.
Mead TJ, Martin DR, Wang LW, Cain SA, Gulec C, Cahill E, Mauch J, Reinhardt D, Lo C, Baldock C, **Apte SS.** Elife. 2022 May 3;11:e71142. doi: 10.7554/eLife.71142.
Corresponding author: aptes@ccf.org
Abstract: *The embryonic extracellular matrix (ECM) undergoes transition to mature ECM as development progresses, yet few mechanisms ensuring ECM proteostasis during this period are known. Fibrillin microfibrils are macromolecular ECM complexes serving structural and regulatory roles. In mice, Fbn1 and Fbn2, encoding the major microfibrillar components, are strongly expressed during embryogenesis, but fibrillin-1 is the major component observed in adult tissue microfibrils. Here, analysis of Adamts6 and Adamts10 mutant mouse embryos, lacking these homologous secreted metalloproteases individually and in combination, along with in vitro analysis of microfibrils, measurement of ADAMTS6-fibrillin affinities and N-terminomics discovery of ADAMTS6-cleaved sites, identifies a proteostatic mechanism contributing to postnatal fibrillin-2 reduction and fibrillin-1 dominance. The lack of ADAMTS6, alone and in combination with ADAMTS10 led to excess fibrillin-2 in perichondrium, with impaired skeletal development defined by a drastic reduction of aggrecan and cartilage link protein, impaired BMP signaling in cartilage, and increased GDF5 sequestration in fibrillin-2-rich tissue. Although ADAMTS6 cleaves fibrillin-1 and fibrillin-2 as well as fibronectin, which provides the initial scaffold for microfibril assembly, primacy of the protease-substrate relationship between ADAMTS6 and fibrillin-2 was unequivocally established by reversal of the defects in Adamts6$^{-/-}$ embryos by genetic reduction of Fbn2, but not Fbn1.*

Forward and reverse degradomics defines the proteolytic landscape of human knee osteoarthritic cartilage and the role of the serine protease HtrA1.
Bhutada S, Li L, Willard B, Muschler G, Piuzzi N, Apte SS. Osteoarthritis Cartilage. 2022 Mar 24:S1063-4584(22)00691-4. doi: 10.1016/j.joca.2022.02.622.
Corresponding author: aptes@ccf.org
Abstract:
Objectives: *Proteolytic destruction of articular cartilage, a major pathogenic mechanism in osteoarthritis (OA), was not previously investigated by terminomics strategies. We defined the degradome of human knee OA cartilage and the contribution therein of the protease HtrA1 using Terminal Amine Isotopic Labeling of Substrates (TAILS).* ***Design:*** *Proteins from OA cartilage taken at knee arthroplasty (n = 6) or separately, from healthy cartilage incubated in triplicate with/without active HtrA1, were labeled at natural and proteolytically cleaved N-termini by reductive dimethylation, followed by trypsin digestion, enrichment of N-terminally labeled/blocked peptides, tandem mass spectrometry and positional peptide annotation to identify cleavage sites. Biglycan proteolysis by HtrA1 was validated biochemically and Amino-Terminal Oriented Mass Spectrometry of Substrates (ATOMS) was used to define the HtrA1 cleavage sites.* ***Results:*** *We identified 10,155 unique internal peptides from 2,162 proteins, suggesting at least 10,797 cleavage sites in OA cartilage. 7,635 internal peptides originated in 371 extracellular matrix/secreted components, many undergoing extensive proteolysis. Rampant ragging of protein termini suggested pervasive exopeptidase activity. HtrA1, the most abundant protease in OA cartilage, experimentally generated 323 cleavages in 109 cartilage proteins, accounting for 171 observed cleavages in the OA degradome. ATOMS identified HtrA1 cleavage sites in a selected substrate, biglycan, whose direct cleavage by HtrA1 was thus orthogonally validated.* ***Conclusions:*** *OA cartilage demonstrates widespread proteolysis by endo- and exopeptidases. HtrA1 contributes broadly to cartilage proteolysis. Forward degradomics of OA cartilage together with reverse degradomics of proteases active in OA, e.g., HtrA1, can potentially fully annotate OA proteolytic pathways and provide new biomarkers.*

Meeting announcements

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List of invited speakers and more detailed information will follow soon!

Contact : antje.steidl@kgu.de; frank.zaucke@kgu.de; www.matrixbiologie.de

The Extracellular Matrix Pharmacology Congress (ECM2022)

Join us at ECM2022 23-25 June 2022, in Copenhagen Denmark. Alterations to the extracellular matrix are a common denominator in most chronic diseases. ECM2022 aims to unlock the potential of the extracellular matrix. The congress will focus on development of new drugs and improve our understanding of the extracellular matrix across chronic diseases. It is time to create a forum for experts to discuss, share and learn from other disease fields!

Session highlights will include:

- The essential components of the ECM
- The importance of ECM in cancer: Barrier for entry or exit?
- Should we treat the ECM or cells in fibrotic diseases?
- The importance of ECM in lung diseases
- The importance of ECM in liver diseases
- Cardiorenal axis and the ECM
- Tissue destruction in inflammatory diseases
- Pharmacological targets of the ECM

- ECM signaling

Speaker highlights:

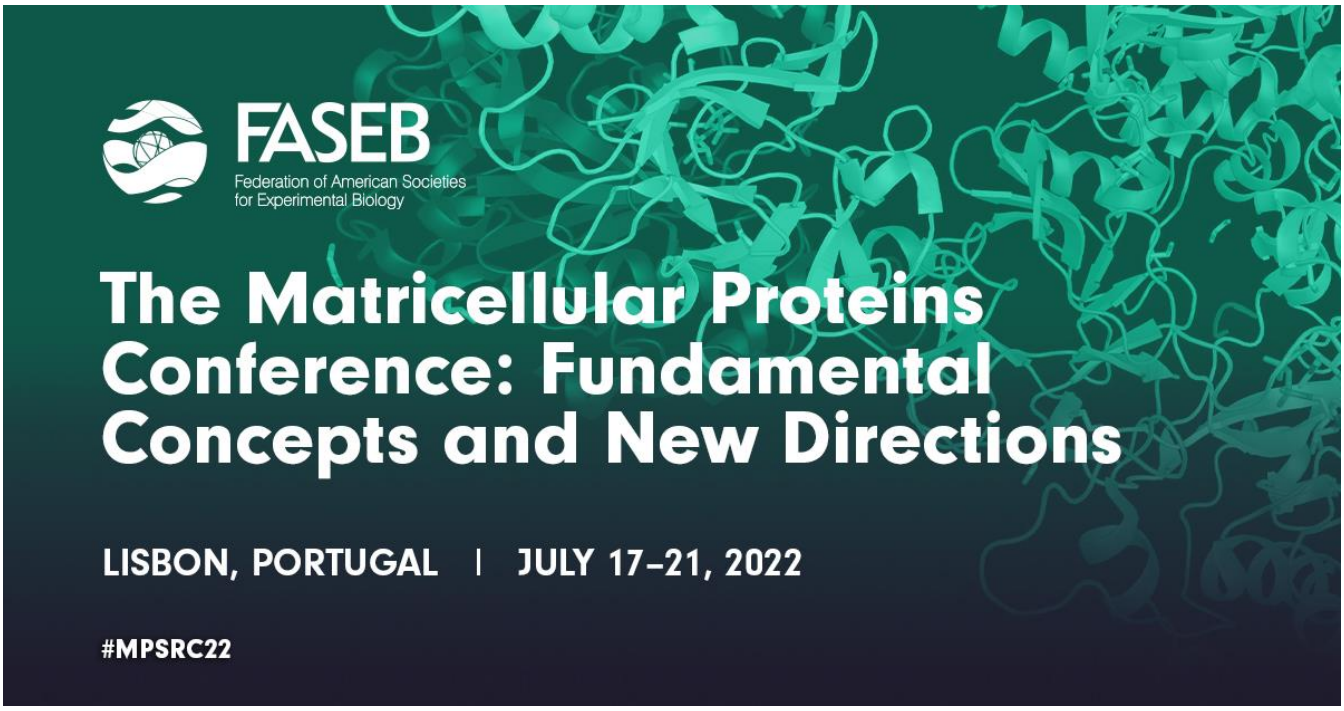
- Valerie Weaver, University of California, USA
- Raghu Kalluri, University of Texas MD Anderson Cancer Center, USA
- Sylvie Ricard-Blum, University of Lyon, France.
- Mina Bissell, Lawrence Berkeley National Laboratory, USA
- Richard O. Hynes, Massachusetts Institute of Technology, US

Proteoglycans GRS (July 9-10, 2022) & GRC (July 10-15, 2022)

Proctor Academy, Andover, NH, USA

https://www.grc.org/proteoglycans-conference/2022/

The Matricellular Proteins Conference: Fundamental Concepts and New Directions
July 17-21, 2022, Lisbon, Portugal



The week of July 17th, the 7th triennial FASEB Science Research Conference (SRC) on Matricellular Proteins organized by Doug Hamilton (University of Western Ontario) and Kurt Hankenson (University of MIchigan) will be held in-person in Lisbon Portugal.

Registration and abstract submission is now open! Selected abstracts will be chosen for open speaker slots (from trainee, early-stage, and/or established investigators). Additionally, abstracts will be presented at two poster sessions.

Please visit this link: https://www.faseb.org/meetings-and-events/src-events/the-matricellular-proteins-conference-functional-concepts-and-new-directions

This conference stands alone as the single opportunity for the matricellular biology community to convene in a highly intellectual and stimulating environment. It facilitates interaction between international scientists from various fields of study and the cross-fertilization of ideas with a renewed perspective. The conference will bring together international scientists from academia, industry, and government who study disease pathogenesis and are curious about the role of secreted, extracellular proteins. The program reinforces the matricellular protein paradigm by reviewing what criteria define matricellular proteins and presents cutting-edge scientific research in matricellular protein biology, particularly expanding a diverse field of new investigators to the field.

Trainees and early-stage investigators in the field of matricellular proteins will find a variety of career development and advancement activities throughout the week.

Join us at the upcoming European Tissue Repair Society meeting in Lyon September 15-17, 2022

Numerous opportunities for early career investigators
Website open for registration & abstract submission http://etrs2022.univ-lyon1.fr/fr

Matrix Biology Europe meeting 2022
September 28-30, 2022, Florence (Italy)

Updates and preliminary program available at https://mbe2022.org/

Dear Colleagues,

The Matrix Biology Europe (MBE) conference is one of the most important congresses in the world addressing extracellular biological polymers, which represent key molecules in several pathophysiological processes.

This international event is held every two years and gives the opportunity to hundreds of senior and young researchers to present their research and to interact with outstanding experts in the field.

Beside the basic science presentations, several sessions are focused on the clinical and biotechnological applications of proteoglycans, which represent very promising targets in human pathology. The program will cover all aspects of the extracellular matrix biology in health and disease, the cell-matrix interactions and signalling, the pathology and tumor environment as well as the advances in matrix disease mechanisms and pharmacological targeting.

The Organizing and Scientific Committees have put together internationally recognized experts as well as younger group leaders as invited speakers. The scientific program will involve several Plenary Lectures and short talks selected from the submitted abstracts.

We really hope to see you again in presence in Florence for a great Congress and it will be a great opportunity to share our experiences after the COVID-19.

We look forward to welcoming you in Florence from 28 to 30 September 2022!

With our best regards,
Alberto G. Passi

Local Organizing Committee

Alberto Passi (President)

Federica Boraldi
Angela D'Ascola
Antonella Forlino
Marilena Formato
Marco Franchi
Evgenia Karousou
Maurizio Onisto
Arianna Parnigoni
Davide Vigetti
Manuela Viola

Scientific board

Stephan Brezillon
University of Reims (France)

Renato Iozzo
Thomas Jefferson University Philadelfia (USA)

Paraskevi Heldin
University of Uppsala (Sweden)

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Sylvie Ricard-Blum
University of Lyon (France)

Irit Sagi
Weizmann Institute (Israel)

Liliana Schaefer
University of Frankfurt (Germany)

Tom Van Agtmael
University of Glasgow (UK)

British Society for Matrix Biology

Autumn BSMB meeting September 12-14, 2022

The Matrix in Development

The British Society for Matrix Biology, and local organiser Dr Blandine Poulet, is pleased to invite you to the next face-to-face **Autumn BSMB meeting in Liverpool**, taking place at the Maritime Museum between the **12th and 14th of September 2022**. A range of national and international speakers will present their recent research on "the matrix in development", and in associated matrix research. In addition, a pre-meeting workshop on the 12th of September will focus on early career researchers and their career, culminating in a networking event: all delegates are invited to attend this event.

Location: Liverpool Maritime Museum
Start date: Sept. 12, 2022
Duration: 2 days
Registration start: June 1, 2022 Registration end date: Sept. 1, 2022 Registration late date: Aug. 21, 2022
Abstract start: June 1, 2022
Abstract end date: Aug. 21, 2022

More detailed information will be published on https://bsmb.ac.uk/meetings/matrix-development/

ASMB workshop October 16-18, 2022
University of Virginia, Charlottesville (USA)

Fibroblast banner image courtesy of Eva Korpos Pintye-Gyuri.

Topics of discussion include cell heterogeneity, patterns of phenotypic differentiation, and how to quantitatively measure fibroblast physiology- as well as career advice and networking opportunities for trainees. If you want to stay up on what's new, this is the workshop for you. Join us!
Organizers: Merry Lindsey, Tom Barker, Kristine DeLeon-Pennell, Lisandra de Castro Brás, Jeremy Simpson, and Daniel Abebayehu
Registration and Abstract submission open in June! Program details are available at:
https://asmb.memberclicks.net/fibroblast-workshop

2023 Collagen Gordon Research Seminar

Colby Sawyer College, NH (USA)
Chairs: Delfien Syx & Jonathan A. Roth
https://www.grc.org/collagen-grs-conference/2021/

2023 Collagen Gordon Research Conference

July 9-14, 2023
Colby Sawyer College, NH (USA)
Chair: Taina Pihlajaniemi
Vice Chair: Douglas B. Gould
https://www.grc.org/collagen-conference/2021/

Gordon Research Conferences
Frontiers of Science

Physiological and Disease Relevance and the Underlaying Molecular Properties of Collagens

- Keynote Session: From 4-Hydroxyproline in Collagen to Hypoxia Control
- Functional Effects and Translational Potential of Mutations in Collagens
- Collagen Transport, Turnover and Homeostasis
- Collagens and Related Molecules in Stem Cell Regulation
- Musculoskeletal Development and Pathology
- Tumor Growth and Metastasis
- Collagens: Systems Approaches, Networks and Interactomes
- Fibrosis and Tissue Repair
- Bioengineering and Materials Design

2023 Elastin, Elastic Fibers & Microfibrils Gordon Research Seminar

Southern New Hampshire University, NH (USA)
Chairs: Muthu Lakshmi Muthu & Kirklann N. Lau
https://www.grc.org/elastin-elastic-fibers-and-microfibrils-grs-conference/2021/

2023 Elastin, Elastic Fibers & Microfibrils Gordon Research Conference

Chair: Dianna Milewicz
Vice Chair: Beth A. Kozel
Southern New Hampshire University, NH (USA)
https://www.grc.org/elastin-elastic-fibers-and-microfibrils-conference/2021/

Gordon Research Conferences
Frontiers of Science

Save these dates!

2023 - October 21-25 ASMB Biennial Meeting

Looking ahead to the next **ASMB Biennial Meeting**, ASMB is pleased to announce that we will be partnering with the American Society for Investigative Pathology and The Histochemical Society for a collaborative meeting in beautiful Salt Lake City, Utah. If you haven't been to this part of the western United States, it is worth a visit! Look for more details of this innovative meeting, "Tissue, Matrix, and Pathobiology: Joint Meeting of ASMB, ASIP, and HCS" coming very soon!
https://asmb.memberclicks.net/meetings

ISMB membership: become a member of ISMB

ISMB is dedicated to promoting matrix biology research on a global scale and to facilitating communication among matrix-related organizations and researchers from different countries. Junior members are eligible for discounted registration fees at matrix biology meetings supported by ISMB. The Society sends out newsletters highlighting recent research advances, descriptions of matrix biology resources, new appointments and awards, together with announcements of relevant meetings.
Every two years, the Society presents the Rupert Timpl Award to a young scientist (<40 years old), who is starting on their independent career, for the best paper related to matrix biology published in the previous two years and gives the Distinguished Investigator Award for lifetime achievement in the field of matrix biology. ISMB sponsors travel grants for young scientists to attend international matrix meetings. If you work in the matrix biology area, consider becoming a member of ISMB to support the international matrix community and give your input on ways to improve interactions and communication. See the website www.ismb.org to join, for recent job postings and newsletters.

Composition of ISMB council subcommittees

Meetings and travel grants
Ruud Bank (The Netherlands, chair)
Gerhard Sengle (Germany)
Hide Watanabe (Japan)

Membership
Hide Watanabe (Japan)
Suneel Apte (USA)

Follow the ISMB on Twitter
ISMB@IntSocMatBio https://twitter.com/intsocmatbio

Communication group coordinated by Julia Etich (Germany, julia.etich@uni-koeln.de)
Valerio Izzi (Finland, Valerio.Izzi@oulu.fi)
Raphael Reuten (Germany, raphael.reuten@pharmakol.uni-freiburg.de)
The ISMB correspondents of National Societies for Matrix Biology for Twitter

ISMB correspondents of National Societies for Matrix Biology for Twitter

The ISMB together with National Societies for Matrix Biology continues to strengthen the visibility of Matrix Biology Research on social media. **Please include @IntSocMatBio on your tweets or contact the representatives of the Societies** (see below). We would be happy to share your announcements with the #MatrixBiology world!

The International Society for Matrix Biology (ISMB) Twitter @IntSocMatBio
Julia Etich, University of Cologne (Germany) julia.etich@uni-koeln.de
Valerio Izzi, University of Oulu (Finland) valerio.Izzi@oulu.fi

The American Society for Matrix Biology (ASMB) Twitter @amsocmatbio
Alexandra Naba, University of Illinois, Chicago (USA) anaba@uic.edu

The British Society for Matrix Biology (BSMB) Twitter @BSMB1
Michal Dudek, University of Manchester (UK) michal.dudek@manchester.ac.uk

The Danish Society for Matrix Biology (DSMB) Twitter @DSMB_dk
Christine Chuang, University of Copenhagen (Denmark) cchuang@sund.ku.dk

The Finnish Connective Tissue Society (FSMB)
Valerio Izzi, University of Oulu (Finland) Valerio.izzi@oulu.fi
Piia Takabe, University of Eastern Finland, Kuopio (Finland) piia.takabe@uef.fi

The French Society for Matrix Biology (SFBMec) Twitter @SFBMEc
Patricia Albanese, University of Créteil (France) albanese@u-pec.fr

The German Society for Matrix Biology (DGMB) **Twitter @Matrixbiologie**
Julian Nüchel, Max Planck Institute for Biology of Ageing, Cologne (Germany) jnuechel@age.mpg.de

Matrix Biology Ireland (MBI) **Twitter @MBIreland**
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Matrix Biology Society of Australia and New Zealand (MBSANZ) **Twitter @MatrixBioANZ**
Luise Kung, Murdoch Childrens Research Institute, Melbourne (Australia) louise.kung@mcri.edu.au

The Swiss Society for Matrix Biology (SSMB) **Twitter @SwissMatrixBio**
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