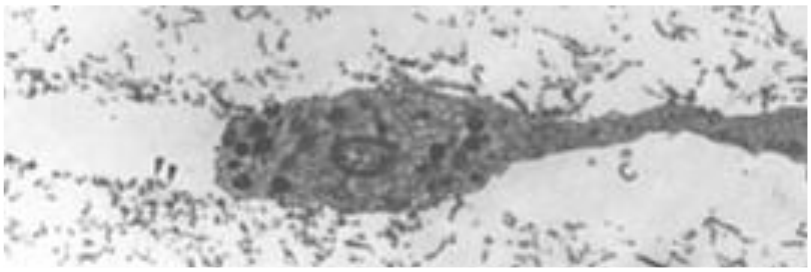


A fibroblast within a tethered lattice, after 13 days, with a cavity surrounding the cell and areas of packed collagen fibrils *(Porter et al. 1998 Wound Rep. Reg. 6: 157-166)*

ISMB NEWSLETTER 39 October 2021 Editor: Sylvie Ricard-Blum

FROM THE PRESIDENT'S DESK

Dear Fellow Matrix Biologists:

The world is experienced a gradual return to normalcy and I hope matters are improving wherever you live and work. In the previous newsletter, I wrote about the value of optimism in the face of the challenge presented to the world by the pandemic and the challenges we may have all faced in our labs and daily lives. The optimism was well-founded, and in large part, a debt is owed to science. I therefore hope you were all able to enjoy some much-deserved, adequate vacation time this summer and could return to fully functioning labs with renewed energy and motivation.

We have all been forced to adapt to the pandemic-modified landscape. One indicator of the new-normal was the ASMB biennial conference, held as a hybrid meeting in St. Louis, MO in September. Congratulations to the ASMB for making this conference happen. I was fortunate to be among the attendees and enjoyed the opportunity to meet colleagues and learn about their work in person. One highlight of this conference is the ISMB Distinguished Investigator Awardee's lecture, and Bob Mecham skillfully blended historical perspective with exciting new data from his lab in his presentation. Another highlight, in my opinion, was the large number of scientists-in-training, indeed constituting the majority of attendees, who without exception, gave high quality presentations and made for animated and informative poster discussions. It was good to see people from different groups mingling with each other, extending the possibility of collaboration, which is such an important benefit of in-person attendance. The hybrid meeting model, may be here to stay. Virtual attendance benefits those who would like to attend, but are unable to do so for a variety of reasons-family or work conflicts, for example. On the other hand, I thought it preferable that speakers should attend in person so they can communicate most effectively and so that the audience can engage them in informal discussions during the conference; their attendance would also minimize technical problems that can potentially derail a conference program. Let's see what 2022 brings in this regard.

Since the last newsletter, Matrix Biology and Matrix Biology Plus have a new editorial team, led by John Whitelock (see more in the newsletter). I echo his thanks to Renato Iozzo, Liliana Schaefer and Nikos Karamanos for their

hard work and dedication to raising the profile of these journals and we wish them well in their respective continuing endeavors. Not all the science world gives sufficient emphasis to matrix biology, but these journals do, and we should all be submitting high-quality research articles regularly to them to sustain and further strengthen them. I hope we will all generously give our time to review for them, since reviews by experts make an immense contribution to the quality of published papers.

Finally, the ISMB website has been rebuilt, thanks to pro bono hard work by Valerio Izzi and his group. ISMB owes them a heartfelt Thank You, and you will read more about this in the newsletter. We are actively seeking volunteers to join the Communications Group and help Val and colleagues shoulder the work of maintaining it. Please visit the website and see it for yourself, and let us know what improvements should be considered. I would be remiss if I did not ask everyone reading the newsletter to visit the website to donate to ISMB, see if you are up to date on your membership, and encourage your colleagues who are not members to join. The ISMB relies largely on member dues to support the travel awards it makes to young scientists and the ISMB prizes and a little bit goes a long way in this effort. Finally, a big thanks to Sylvie for compiling the newsletter. It's not an easy task, so I hope you enjoy reading it.

I wish you good health, happiness and a productive and exciting time at work.

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

Content

News from Matrix Biology & Matrix Biology Plus

Dear Fellow Matrix Biologists,

As the new Editor-In-Chief of Matrix Biology and Matrix Biology Plus, I want to reach out to you all with an update on the changes and plans for Matrix Biology and Matrix Biology Plus. First, I wanted to thank and acknowledge the extraordinary efforts of the previous Editor-in-Chief, Renato Iozzo, and the Deputy Editors, Liliana Schaefer and Nikos Karamanos, for moving and growing Matrix Biology to where it is now, in such a strong position. Since taking the helm, I have had the great fortune to be joined on the Editorial team by three eminent matrix biologists and would like to take this opportunity to welcome Joanne Murphy-Ullrich, Sylvie Ricard-Blum and Suneel Apte as Editors. In the coming months we plan to expand the Editorial Board in a way that represents our demographics, geography, and diversity of scientific disciplines to support our goal of increasing the number of research articles submitted to the journal whilst maintaining the quality of all published papers. The Editors and Editorial Board are receptive to all relevant research that involves the extracellular matrix in biology, disease, cell-matrix interactions and bioengineering and are focused above all on quality, originality, and value of the work. I would like to encourage colleagues from the matrix biology communities around the world to express an interest in joining the Board and be willing to provide expert reviews when sought by the Editors.

The Editorial team is also looking for feedback regarding the on-line companion journal, Matrix Biology Plus, particularly with respect to the types of articles and content. Some suggestions that we have had so far include detailed methods papers, new transgenic models, biomaterials or theoretical/computational models, letters, commentaries and short communications, interdisciplinary research results and large data sets from genomic and proteomic studies focused on matrix biology.
I am looking forward to working with the Editors and Editorial Board into the future to continue to publish high-quality manuscripts that are of significant interest to the international matrix biology community and readership of the Journal. I would like to encourage you all to submit your next paper focused on the matrix for review at Matrix Biology or Matrix Biology Plus.

Yours sincerely,

John Whitelock
Editor-in-Chief
Matrix Biology and Matrix Biology Plus

The new web site of the ISMB

ISMB has a completely new and redesigned website thanks to Valerio Izzi (University of Oulu, Finland). In the spring of 2020, an attack to the platform hosting our website made it unusable, so we took the chance to revamp our webpages and migrate to a more modern platform. Subscriptions and payment are, for example, now handled online without long forms to compile and send. Likewise, grant applications are fully online, speeding up both the submission and the evaluation process! Most importantly, we have a member-only area with special discounts on great ECM content sponsored by ISMB!

As ISMB member you can register for the right to access the member-only area. Simply visit the website and click the “Log in or Sign up” button on the top right corner, then click “New to this site? Sign Up” and register. Our communication team will review your request and grant you access to the restricted content.

See you at www.ismb.org!

Valerio Izzi (seated, second from left), University of Oulu (Finland) and his group

ASMB meeting & Distinguished Investigator Award

The Hybrid American Society for Matrix Biology Biennial Meeting in St. Louis, Missouri (USA)

By Jeff Miner, with assistance from Cindy Ritter

The biennial meeting of the American Society for Matrix Biology (ASMB), which was postponed from November 2020 because of the pandemic, was held September 12-15, both in person at the Hyatt Regency St. Louis at the Arch and virtually via live and recorded streaming. The meeting was chaired by ASMB President-Elect Jeff Miner of Washington University School of Medicine in St. Louis and drew approximately 160 in-person attendees and 160 remote attendees. This event satisfied the hunger of matrix biologists for a live meeting. There were many graduate students present who had never attended a live scientific conference before.

The sessions highlighted the latest advances in extracellular matrix biology research. Ken Yamada from the National Institutes of Health provided an outstanding Keynote address. Many of the invited speakers, particularly those from Canada, Europe, and Asia, participated via Zoom. All attendees were vaccinated, and masks were required unless lecturing, eating, or drinking.

An emphasis of the meeting was to support the career development of junior faculty and trainees and to enhance diversity within the matrix biology research community. Junior scientists co-chaired the 17 concurrent sessions and had access to mentoring and networking opportunities. In addition, the new Iozzo Trainee Awards endowed by a generous gift from Renato Iozzo, were established for a graduate student and a postdoctoral fellow who demonstrate outstanding contributions to the field. The inaugural winner of the 2021 Iozzo Trainee Award for a graduate student was Sarah Lipp from Purdue University, and the winner in the postdoc category was Nandaraj Taye from Icahn School of Medicine at Mount Sinai New York.

In addition to the Iozzo Trainee Awards, there were five other awards presented. The ASMB presented its Senior Investigator Award to William Parks of Cedars-Sinai Medical Center; its Junior Investigator Award to Ashley Brown of North Carolina State University and the University of North Carolina-Chapel Hill; its Iozzo Award to Jessica Wagenseil of Washington University in St. Louis; and its Founders Award to Heena Kumra of McGill University. The ISMB Distinguished Investigator Award was presented to Robert Mecham of Washington University School of Medicine in St. Louis.

In a special session, Nikki Doughty of Washington University in St. Louis's Institute for School Partnership lectured about the importance of diversity equity, and inclusion in science, technology, engineering, and mathematics (STEM) fields. Ms. Doughty brought six St. Louis area underrepresented minority high school students to the meeting to interact with matrix biologists at Monday's poster session.
Regarding non-scientific activities, attendees took part in an early morning 5K run/walk around the Gateway Arch grounds. In addition, there was a well-attended social event at Ballpark Village's Crown Room overlooking Busch Baseball Stadium on Tuesday evening, where corn hole, Jenga, and Connect4 games were enjoyed by many.

Robert Mecham (Washington University School of Medicine, St. Louis, Missouri, USA) was given the Distinguished Investigator Award 2020 at ASMB meeting in St Louis. We warmly congratulate him for his achivement in understanding the complex process of extracellular matrix secretion and assembly, with a particular focus on ECM proteins important to the cardiovascular system including elastin.

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@kgu.de)

In Focus

A microenvironment-inspired synthetic three-dimensional model for pancreatic ductal adenocarcinoma organoids

Below CR, Kelly J, Brown A, Humphries JD, Hutton C, Xu J, Lee BY, Cintas C, Zhang X, Hernandez-Gordillo V, Stockdale L, Goldsworthy MA, Geraghty J, Foster L, O'Reilly DA, Schedding B, Askari J, Burns J, Hodson N, Smith DL, Lally C, Ashton G, Knight D, Mironov A, Banyard A, Eble JA, Morton JP, Humphries MJ, Griffith LG, Jørgensen C. Nat Mater. 2021 Sep 13. doi: 10.1038/s41563-021-01085-1.

Corresponding author: griff@mit.edu and claus.jorgensen@manchester.ac.uk

Abstract: *Experimental in vitro models that capture pathophysiological characteristics of human tumours are essential for basic and translational cancer biology. Here, we describe a fully synthetic hydrogel extracellular matrix designed to elicit key phenotypic traits of the pancreatic environment in culture. To enable the growth of normal and cancerous pancreatic organoids from genetically engineered murine models and human patients, essential adhesive cues were empirically defined and replicated in the hydrogel scaffold, revealing a functional role of laminin-integrin α_3/α_6 signalling in establishment and survival of pancreatic organoids. Altered tissue stiffness-a hallmark of pancreatic cancer-was recapitulated in culture by adjusting the hydrogel properties to engage mechano-sensing pathways and alter organoid growth. Pancreatic stromal cells were readily incorporated into the hydrogels and replicated phenotypic traits characteristic of the tumour environment in vivo. This model therefore recapitulates a pathologically remodelled tumour microenvironment for studies of normal and pancreatic cancer cells in vitro.*

Homogenous overexpression of the extracellular matrix protein Netrin-1 in a hollow fiber bioreactor

Moya-Torres A, Gupta M, Heide F, Krahn N, Legare S, Nikodemus D, Imhof T, Meier M, Koch M, Stetefeld J. Appl Microbiol Biotechnol. 2021 Aug;105(14-15):6047-6057. doi: 10.1007/s00253-021-11438-0.

Corresponding author: heidef@myumanitoba.ca and jorg.stetefeld@umanitoba.ca

Abstract: *The production of recombinant proteins for functional and biophysical studies, especially in the field of structural determination, still represents a challenge as high quality and quantities are needed to adequately perform experiments. This is in part solved by optimizing protein constructs and expression conditions to maximize the yields in regular flask expression systems. Still, work flow and effort can be substantial with no guarantee to obtain improvements. This study presents a combination of workflows that can be used to dramatically increase protein production and improve processing results, specifically for the extracellular matrix protein Netrin-1. This proteoglycan is an axon guidance cue which interacts with various receptors to initiate downstream signaling cascades affecting cell differentiation, proliferation, metabolism, and survival. We were able to produce large glycoprotein quantities in mammalian cells, which were engineered for protein overexpression and secretion into*

the media using the controlled environment provided by a hollow fiber bioreactor. Close monitoring of the internal bioreactor conditions allowed for stable production over an extended period of time. In addition to this, Netrin-1 concentrations were monitored in expression media through biolayer interferometry which allowed us to increase Netrin-1 media concentrations tenfold over our current flask systems while preserving excellent protein quality and in solution behavior. Our particular combination of genetic engineering, cell culture system, protein purification, and biophysical characterization permitted us to establish an efficient and continuous production of high-quality protein suitable for structural biology studies that can be translated to various biological systems.

A novel in vitro assay to study chondrocyte-to-osteoblast transdifferentiation

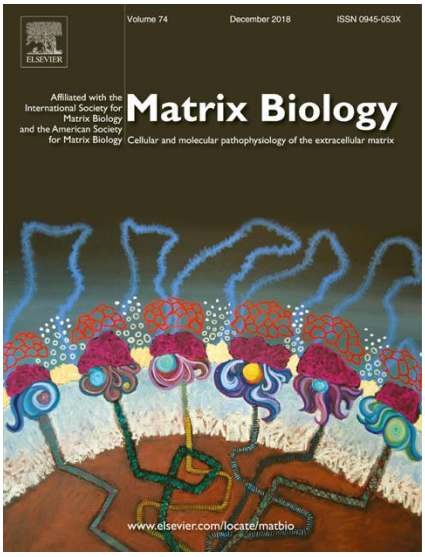
Tschaffon MEA, Reber SO, Schoppa A, Nandi S, Cirstea IC, Aszodi A, Ignatius A, Haffner-Luntzer M. Endocrine. 2021 Sep 16. doi: 10.1007/s12020-021-02853-4.

Corresponding author: melanie.haffner-luntzer@uni-ulm.de

Abstract: ***Purpose:*** *Endochondral ossification, which involves transdifferentiation of chondrocytes into osteoblasts, is an important process involved in the development and postnatal growth of most vertebrate bones as well as in bone fracture healing. To study the basic molecular mechanisms of this process, a robust and easy-to-use in vitro model is desirable. Therefore, we aimed to develop a standardized in vitro assay for the transdifferentiation of chondrogenic cells towards the osteogenic lineage.* ***Methods:*** *Murine chondrogenic ATDC5 cells were differentiated into the chondrogenic lineage for seven days and subsequently differentiated towards the osteogenic direction. Gene expression analysis of pluripotency, as well as chondrogenic and osteogenic markers, cell-matrix staining, and immunofluorescent staining, were performed to assess the differentiation. In addition, the effects of Wnt3a and lipopolysaccharides (LPS) on the transdifferentiation were tested by their addition to the osteogenic differentiation medium.* ***Results:*** *Following osteogenic differentiation, chondrogenically pe-differentiated cells displayed the expression of pluripotency and osteogenic marker genes as well as alkaline phosphatase activity and a mineralized matrix. Co-expression of Col2a1 and Col1a1 after one day of osteogenic differentiation indicated that osteogenic cells had differentiated from chondrogenic cells. Wnt3a increased and LPS decreased transdifferentiation towards the osteogenic lineage.* ***Conclusion:*** *We successfully established a rapid, standardized in vitro assay for the transdifferentiation of chondrogenic cells into osteogenic cells, which is suitable for testing the effects of different compounds on this cellular process.*

Books & Special Issues on the Extracellular Matrix

Beyond the Matrisome: New Frontiers in ECM Research
A Special Issue of *Matrix Biology*
Edited by Alexandra Naba and Suneel Apte



2021 marks a decade since conception and delineation of the matrisome, which provided a road map for extracellular matrix research. To start the next decade, Matrix Biology will host a Special Issue titled “Beyond the Matrisome: New Frontiers in ECM Research” guest-edited by Alexandra Naba and Suneel Apte.
The overall goal of the Special Issue is a forward-looking view of the matrisome illustrated by state-of-the-art invited reviews and conceptually novel and preferably mechanistic research articles.

Research articles submitted for consideration for the Special Issue can span the full band-width of -omic applications for mechanistic ECM research, new developments in understanding molecular networks within the ECM, or mechanistic studies on ECM molecules and complexes, covering the breadth of the field from fundamental molecular sciences to applications to development, diseases and tissue engineering. Matrix Biology invites you to contribute a research article for this upcoming Special Issue, offering the quality, visibility and impact that you would expect from the flagship journal in ECM research, combined with the convenience and reach of open access. Articles are published online, quickly after acceptance, and constantly so there are no print delays or long waits for publication. The deadline for manuscript submission for consideration for the Special Issue is January 31, 2022.

Manuscripts judged on initial review by the special issue co-editors to not fit well with the intended scope of the issue will be redirected into the regular manuscript stream of Matrix Biology.

Please remember the following items:

- Please make sure that you select the name of the Special Issue when you upload your manuscript: Please, mention this on the top of your cover letter as well:
- Include the names and emails of four potential expert reviewers. All the manuscripts will be peer-reviewed.
- Please follow the recommended Matrix Biology style.
- Include the mandatory Highlights, in bullet form with 87 characters maximum.

Thank you very much in advance for your contribution to this special issue of Matrix Biology.

Best wishes.

Alexandra Naba, PhD, University of Illinois-Chicago, USA
Suneel S. Apte, MBBS, DPhil, Cleveland Clinic Lerner Research Institute., Cleveland, USA

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

THEmeshwork

#THEmeshwork went REAL at ASMB 2021

As we are slowly adapting to the new world, ASMB just ran an amazing HYDRID meeting in-person/virtual. At this occasion, Tia and I met for the first time in person after a year working together for #THEmeshwork, what a satisfaction!

For reminder, in September 2020, we created #THEmeshwork, a Slack platform to connect and serve the early-career researchers and organized monthly zoom events during the pandemic.

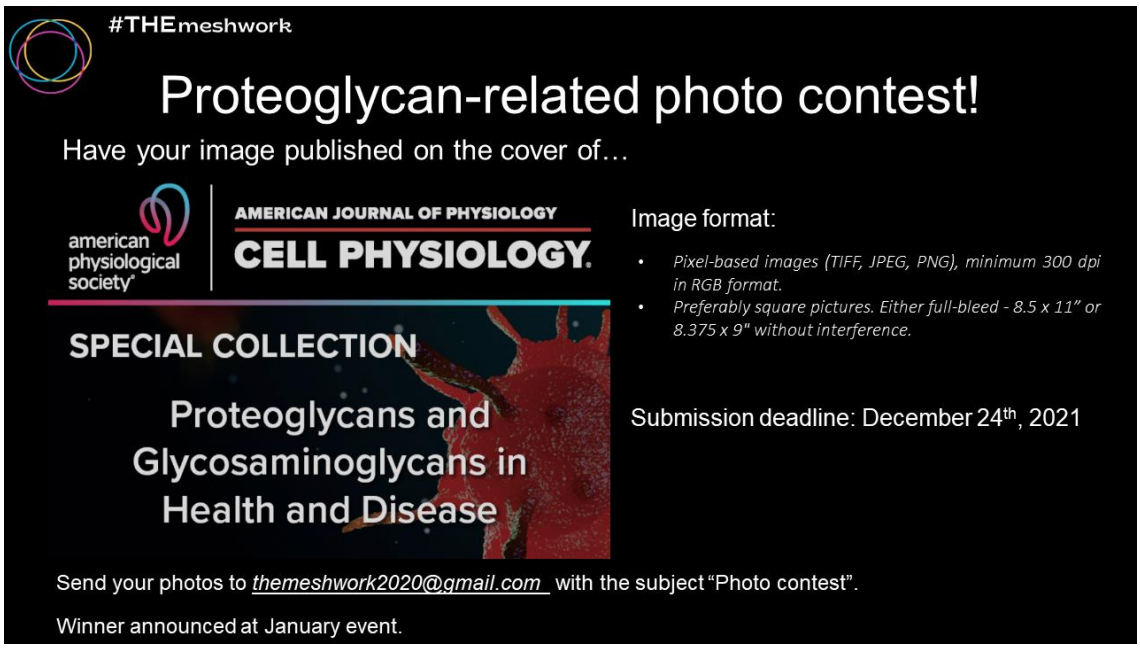
As meeting are now coming back, we are working toward new crazy ideas for #THEmeshwork. We are now an official non-profit organization and look forward to a bright future to help young researchers as they figure out their career path.

Tia Jones and Julie Di Martino running #THEmeshwork event at ASMB 2021

At ASMB 2021, with the support of their executive committee and thanks to the amazing Kendra LaDuca, we gathered a group of early-career researchers and introduce them to our initiative. 20 new members joined #THEmeshwork and we are now proud to connect 220 early-career researchers around the world.

If you didn't join yet, email us at **themeshwork2020@gmail.com**, visit our website **https://themeshwork2020.wixsite.com/info** . We have opened positions to be part of the organizers group so don't hesitate to get involved and develop your leadership skills. Finally, we recently created our official twitter account, follow us to stay tuned on our new initiatives to come **@THEmeshwork2020**

Julie on the behalf of THEmeshwork organization



International travel grants

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.

Recent publications

Giantin is required for intracellular N-terminal processing of type I procollagen. Stevenson NL, Bergen DJM, Lu Y, Prada-Sanchez ME, Kadler KE, Hammond CL, Stephens DJ. J Cell Biol. 2021 Jun 7;220(6):e202005166. doi: 10.1083/jcb.202005166.
Corresponding author: nicola.stevenson@bristol.ac.uk and david.stephens@bristol.ac.uk
Abstract: *Knockout of the golgin giantin leads to skeletal and craniofacial defects driven by poorly studied changes in glycosylation and extracellular matrix deposition. Here, we sought to determine how giantin impacts the production of healthy bone tissue by focusing on the main protein component of the osteoid, type I collagen. Giantin mutant zebrafish accumulate multiple spontaneous fractures in their caudal fin, suggesting their bones may be more brittle. Inducing new experimental fractures revealed defects in the mineralization of newly deposited collagen as well as diminished procollagen reporter expression in mutant fish. Analysis of a human giantin knockout cell line expressing a GFPtagged procollagen showed that procollagen trafficking is independent of giantin. However, our data show that intracellular N-propeptide processing of pro-α1(I) is defective in the absence of giantin. These data demonstrate a conserved role for giantin in collagen biosynthesis and extracellular matrix assembly. Our work also provides evidence of a giantin-dependent pathway for intracellular procollagen processing.*

Extracellular matrix-based cancer targeting. Karamanos NK, Piperigkou Z, Passi A, Götte M, Rousselle P, Vlodavsky I. Trends in Molecular Medicine. 2021 Oct;27(10):1000-1013. doi: 10.1016/j.molmed.2021.07.009.
Corresponding author: n.k.karamanos@upatras.gr
Abstract: *Tumor extracellular matrix (ECM) operates in a coordinated mode with cancer and stroma cells to evoke the multistep process of metastatic potential. The remodeled tumor-associated matrix provides a point for direct or complementary therapeutic targeting. Here, we cover and critically address the importance of ECM networks and their macromolecules in cancer. We focus on the roles of key structural and functional ECM components, and their degradation enzymes and extracellular vesicles, aiming at improving our understanding of the mechanisms contributing to tumor initiation, growth, and dissemination, and discuss potential new approaches for ECM-based therapeutic targeting and diagnosis.*

Laminin Polymerization and Inherited Disease: Lessons From Genetics (Mini review) Liam Shaw, Conor J. Sugden and Kevin J. Hamill. Front. Genet., 12 August 2021 | https://doi.org/10.3389/fgene.2021.707087
Corresponding author: khamill@liverpool.ac.uk
Abstract*: The laminins (LM) are a family of basement membranes glycoproteins with essential structural roles in supporting epithelia, endothelia, nerves and muscle adhesion, and signaling roles in regulating cell migration, proliferation, stem cell maintenance and differentiation. Laminins are obligate heterotrimers comprised of α, β and γ chains that assemble intracellularly. However, extracellularly these heterotrimers then assemble into higher-order networks via interaction between their laminin N-terminal (LN) domains. In vitro protein studies have identified assembly kinetics and the structural motifs involved in binding of adjacent LN domains. The physiological importance of these interactions has been identified through the study of pathogenic point mutations in LN domains that lead to syndromic disorders presenting with phenotypes dependent on which laminin gene is mutated. Genotype-phenotype comparison between knockout and LN domain missense mutations of the same laminin allows inferences to be drawn about the roles of laminin network assembly in terms of tissue function. In this review, we will discuss these comparisons in terms of laminin disorders, and the therapeutic options that understanding these processes have allowed. We will also discuss recent findings of non-laminin mediators of laminin network assembly and their implications in terms of basement membrane structure and function.*

Extended disorder at the cell surface: The conformational landscape of the ectodomains of syndecans. Gondelaud F, Bouakil M, Le Fèvre A, Miele AE, Chirot F, Duclos B, Liwo A, Ricard-Blum S Matrix Biol Plus. 2021 Jul 19;12:100081. doi: 10.1016/j.mbplus.2021.100081.
Corresponding author: sylvie.ricard-blum@univ-lyon1.fr
Abstract: *Syndecans are membrane proteoglycans regulating extracellular matrix assembly, cell adhesion and signaling. Their ectodomains can be shed from the cell surface, and act as paracrine and autocrine effectors or as competitors of full-length syndecans. We report the first biophysical characterization of the recombinant ectodomains of the four human syndecans using biophysical techniques, and show that they behave like flexible random-coil intrinsically disordered proteins, and adopt several conformation ensembles in solution. We have characterized their conformational landscapes using native mass spectrometry (MS) and ion-mobility MS, and demonstrated that the syndecan ectodomains explore the majority of their conformational landscape, from minor compact, globular-like, conformations to extended ones. We also report that the ectodomain of syndecan-4, corresponding to a natural isoform, is able to dimerize via a disulfide bond. We have generated a three-dimensional model of the C-terminus of this dimer, which supports the dimerization via a disulfide bond. Furthermore, we have mapped the NXIP adhesion motif of syndecans and their sequences involved in the formation of ternary complexes with integrins and growth factor receptors on the major conformations of their ectodomains, and shown that these sequences are not accessible in all the conformations, suggesting that only some of them are biologically active. Lastly, although the syndecan ectodomains have a far lower number of amino*

acid residues than their membrane partners, their intrinsic disorder and flexibility allow them to adopt extended conformations, which have roughly the same size as the cell surface receptors (e.g., integrins and growth factor receptors) they bind to.

Tropoelastin promotes the formation of dense, interconnected endothelial networks. Al Halawani, A., Abdulkhalek L., Mithieux S.M. and Weiss A.S. Biomolecules 2021 Sep 6;11(9):1318.doi: 10.3390/biom11091318.
Corresponding authors: allen.alhalawani@sydney.edu.au, lea.abdul@gmail.com, suzanne.mithieux@sydney.edu.au
Abstract: *Tropoelastin, the soluble precursor of elastin, has been used for regenerative and wound healing purposes and noted for its ability to accelerate wound repair by enhancing vascularization at the site of implantation. However, it is not clear whether these effects are directly due to the interaction of tropoelastin with endothelial cells or communicated to endothelial cells following interactions between tropoelastin and neighboring cells, such as mesenchymal stem cells (MSCs). We adapted an endothelial tube formation assay to model in vivo vascularization with the goal of exploring the stimulatory mechanism of tropoelastin. In the presence of tropoelastin, endothelial cells formed less tubes, with reduced spreading into capillary-like networks. In contrast, conditioned media from MSCs that had been cultured on tropoelastin enhanced the formation of more dense, complex, and interconnected endothelial tube networks. This pro-angiogenic effect of tropoelastin is mediated indirectly through the action of tropoelastin on co-cultured cells. We conclude that tropoelastin inhibits endothelial tube formation, and that this effect is reversed by pro-angiogenic crosstalk from tropoelastin-treated MSCs. Furthermore, we find that the known in vivo pro-angiogenic effects of tropoelastin can be modeled in vitro, highlighting the value of tropoelastin as an indirect mediator of angiogenesis.*

Fuzzy binding model of molecular interactions between tropoelastin and integrin alphavbeta3. Ozsvar, J., Wang, R., Tarakanova, A., Buehler, M.J. and Weiss, A.S. Biophys J 2021 Aug 3;120(15):3138-3151. doi: 10.1016/j.bpj.2021.04.037.
Corresponding author: tony.weiss@sydney.edu.au
Abstract: *Tropoelastin is the highly flexible monomer subunit of elastin, required for the resilience of the extracellular matrix in elastic tissues. To elicit biological signaling, multiple sites on tropoelastin bind to cell surface integrins in a poorly understood multifactorial process. We constructed a full atomistic molecular model of the interactions between tropoelastin and integrin αvβ3 using ensemble-based computational methodologies. Conformational changes of integrin αvβ3 associated with outside-in signaling were more frequently facilitated in an ensemble in which tropoelastin bound the integrin's α1 helix rather than the upstream canonical binding site. Our findings support a model of fuzzy binding, whereby many tropoelastin conformations and defined sites cooperatively interact with multiple αvβ3 regions. This model explains prior experimental binding to distinct tropoelastin regions, domains 17 and 36, and points to the cooperative participation of domain 20. Our study highlights the utility of ensemble-based approaches in helping to understand the interactive mechanisms of functionally significant flexible proteins.*

Domains 12 to 16 of tropoelastin promote cell attachment and spreading through interactions with glycosaminoglycan and integrins alphav and alpha5beta1. Bochicchio, B., Yeo, G.C., Lee, P., Emul, D., Pepe, A., Laezza, A., Ciarfaglia, N., Quaglino, D. and Weiss, A.S. FEBS J. 2021 Jul;288(13):4024-4038. doi: 10.1111/febs.15702
Corresponding author: giselle.yeo@sydney.edu.au, tony.weiss@sydney.edu.au
Abstract: *Elastin is an extracellular matrix component with key structural and biological roles in elastic tissues. Interactions between resident cells and tropoelastin, the monomer of elastin, underpin elastin's regulation of cellular processes. However, the nature of tropoelastin-cell interactions and the contributions of individual*

tropoelastin domains to these interactions are only partly elucidated. In this study, we identified and characterized novel cell-adhesive sites in the tropoelastin N-terminal region between domains 12 and 16. We found that this region interacts with αV and α5β1 integrin receptors, which mediate cell attachment and spreading. A peptide sequence from within this region, spanning domains 14 to mid-domain 16, binds heparan sulfate through electrostatic interactions with peptide lysine residues and induces conformational ordering of the peptide. We propose that domains 14-16 direct initial cell attachment through cell-surface heparan sulfate glycosaminoglycans, followed by αV and α5β1 integrin-promoted attachment and spreading on domains 12-16 of tropoelastin. These findings advance our mechanistic understanding of elastin matrix biology, with the potential to enhance tissue regenerative outcomes of elastin-based materials.

Investigation of the Structure of Regulatory Proteins Interacting with Glycosaminoglycans by Combining NMR Spectroscopy and Molecular Modeling – The Beginning of a Wonderful Friendship. Künze G., Huster D., Samsonov S.A. Biol Chem 2021 Apr 21. doi: 10.1515/hsz-2021-0119. Online ahead of print.
Corresponding author: daniel.huster@medizin.uni-leipzig.de
Abstract: *The interaction of regulatory proteins with extracellular matrix or cell surface-anchored glycosaminoglycans (GAGs) plays important roles in molecular recognition, wound healing, growth, inflammation and many other processes. In spite of their high biological relevance, protein-GAG complexes are significantly underrepresented in structural databases because standard tools for structure determination experience difficulties in studying these complexes. Co-crystallization with subsequent X-ray analysis is hampered by the high flexibility of GAGs. NMR spectroscopy experiences difficulties related to the periodic nature of the GAGs and the sparse proton network between protein and GAG with distances that typically exceed the detection limit of nuclear Overhauser enhancement spectroscopy. In contrast, computer modeling tools have advanced over the last years delivering specific protein-GAG docking approaches successfully complemented with molecular dynamics (MD)-based analysis. Especially the combination of NMR spectroscopy in solution providing sparse structural constraints with molecular docking and MD simulations represents a useful synergy of forces to describe the structure of protein-GAG complexes. Here we review recent methodological progress in this field and bring up examples where the combination of new NMR methods along with cutting-edge modeling has yielded detailed structural information on complexes of highly relevant cytokines with GAGs.*

Computational insights into heparin-small molecule interactions: evaluation of the balance between stacking and non-stacking binding modes. Maszota-Zieleniak M., Zsila F., Samsonov S.A. Carbohydr Res 2021 Sep;507:108390. doi: 10.1016/j.carres.2021.108390.
Corresponding author : sergey.samsonov@ug.edu.pl
Abstract: *Glycosaminoglycans (GAGs), anionic periodic linear polysaccharides, are involved in a manifold of key biochemical processes ongoing in the extracellular matrix via establishing direct intermolecular interactions with diverse classes of biopolymers as well as with bioactive small molecules. Due to their acidic nature, they are capable of binding positively charged ligands, which, in turn could affect their binding with protein and peptide targets, modulating a number of physiologically important signaling pathways. Therefore, it is of great significance to improve our understanding on the molecular basis underlying GAG-small molecule interactions. In this study, we applied in silico approaches (molecular dynamics and free energy calculations) complemented with circular dichroism and absorption spectroscopy to characterize the complex formation between heparin, one of the principal members of GAG family, and twenty different cationic ligands including therapeutic drugs, alkaloids and organic dyes. In particular, the oligomerization propensity of ligands prior to heparin binding, binding free energy parameters, effects of the ionic strength are rigorously described. Based on the performed analysis, the ligands are classified into three main groups depending on their heparin binding and oligomerization properties.*

The computational data agree and provide rationale for the corresponding experimental findings, contributing to the general knowledge of the physico-chemical nature of ligand-GAG intermolecular interactions.

The potential role of glycosaminoglycans in serum amyloid A fibril formation by in silico approaches. Maszota-Zieleniak M., Danielsson A., Samsonov S.A. Matrix Biol Plus 2021 Jul 22;12:100080. doi: 10.1016/j.mbplus.2021.100080.
Corresponding author: sergey.samsonov@ug.edu.pl
Abstract: *Serum amyloid A (SAA) is actively involved in such pathological processes as atherosclerosis, rheumatoid arthritis, cancer and Alzheimer's disease by its aggregation. One of the factors that can attenuate its aggregation and so affects its physiological role is its interactions with glycosminoglycans (GAGs), linear anionic periodic polysaccharides. These molecules located in the extracellular matrix of the cell are highly variable in their chemical composition and sulfation patterns. Despite the available experimental evidence of SAA-GAG interactions, no mechanistic details at atomic level have been reported for these systems so far. In our work we aimed to apply diverse computational tools to characterize SAA-GAG complexes formation and to answer questions about their potential specificity, energetic patterns, particular SAA residues involved in these interactions, favourable oligomeric state of the protein and the potential influence of GAGs on SAA aggregation. Molecular docking, conventional and replica exchange molecular dynamics approaches were applied to corroborate the experimental knowledge and to propose the corresponding molecular models. SAA-GAG complex formation was found to be electrostatics-driven and rather unspecific of a GAG sulfation pattern, more favorable for the dimer than for the monomer when binding to a short GAG oligosaccharide through its N-terminal helix, potentially contributing to the unfolding of this helix, which could lead to the promotion of the protein aggregation. The data obtained add to the specific knowledge on SAA-GAG systems and deepen the general understanding of protein-GAG interactions that is of a considerable value for the development of GAG-based approaches in a broad therapeutic context.*

Modeling protein-glycosaminoglycan complexes: does the size matter? Marcisz M., Zacharias M., Samsonov S.A. J Chem Inf Model. 2021 Sep 27;61(9):4475-4485. doi: 10.1021/acs.jcim.1c00664.
Corresponding author: sergey.samsonov@ug.edu.pl
Abstract: *Docking glycosaminoglycans (GAGs) has been challenging because of the complex nature of these long periodic linear and negatively charged polysaccharides. Although standard docking tools like Autodock3 are successful when docking GAGs up to hexameric length, they experience challenges to properly dock longer GAGs. Similar limitations concern other docking approaches typically developed for docking ligands of limited size to proteins. At the same time, most of more advanced docking approaches are challenging for a user who is inexperienced with complex in silico methodologies. In this work, we evaluate the binding energies of complexes with different lengths of GAGs using all-atom molecular dynamics simulations. Based on this analysis, we propose a new docking protocol for long GAGs that consists of conventional docking of short GAGs and further elongation with the use of a coarse-grained representation of the GAG parts not being in direct contact with its protein receptor. This method automated by a simple script is straightforward to use within the Autodock3 framework but also useful in combination with other standard docking tools. We believe that this method with some minor case-specific modifications could also be used for docking other linear charged polymers.*

Advanced Molecular Dynamics Approaches to Model a Tertiary Complex APRIL/TACI with Long Glycosaminoglycans. Marcisz M., Maszota-Zieleniak M., Huard B., Samsonov S.A. Biomolecules. 2021 Sep 12;11(9):1349. doi: 10.3390/biom11091349.
Corresponding author: sergey.samsonov@ug.edu.pl
Abstract *Glycosaminoglycans (GAGs) are linear anionic periodic polysaccharides participating in a number of biologically relevant processes in the extracellular matrix via interactions with their protein targets. Due to their*

periodicity, conformational flexibility, pseudo-symmetry of the sulfation pattern, and the key role of electrostatics, these molecules are challenging for both experimental and theoretical approaches. In particular, conventional molecular docking applied for GAGs longer than 10-mer experiences severe difficulties. In this work, for the first time, 24- and 48-meric GAGs were docked using all-atomic repulsive-scaling Hamiltonian replica exchange molecular dynamics (RS-REMD), a novel methodology based on replicas with van der Waals radii of interacting molecules being scaled. This approach performed well for proteins complexed with oligomeric GAGs and is independent of their length, which distinguishes it from other molecular docking approaches. We built a model of long GAGs in complex with a proliferation-inducing ligand (APRIL) prebound to its receptors, the B cell maturation antigen and the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI). Furthermore, the prediction power of the RS-REMD for this tertiary complex was evaluated. We conclude that the TACI–GAG interaction could be potentially amplified by TACI's binding to APRIL. RS-REMD outperformed Autodock3, the docking program previously proven the best for short GAGs.

Lasp1 regulates adherens junction dynamics and fibroblast transformation in destructive arthritis. Beckmann D, Römer-Hillmann A, Krause A, Hansen U, Wehmeyer C, Intemann J, de Gorter DJJ, Dankbar B, Hillen J, Heitzmann M, Begemann I, Galic M, Weinhage T, Foell D, Ai R, Kremerskothen J, Kiener HP, Müller S, Kamradt T, Schröder C, Leitão E, Horsthemke B, Rosenstiel P, Nordström K, Gasparoni G, Gasparoni N, Walter J, Li N, Yang X, Chung HR, Pavenstädt H, Lindemann N, Schnittler HJ, Wang W, Firestein GS, Pap T, Korb-Pap A. Nat Commun. 2021 Jun 15;12(1):3624. doi: 10.1038/s41467-021-23706-8.
Corresponding author: korba@uni-muenster.de
Abstract: *The LIM and SH3 domain protein 1 (Lasp1) was originally cloned from metastatic breast cancer and characterised as an adaptor molecule associated with tumourigenesis and cancer cell invasion. However, the regulation of Lasp1 and its function in the aggressive transformation of cells is unclear. Here we use integrative epigenomic profiling of invasive fibroblast-like synoviocytes (FLS) from patients with rheumatoid arthritis (RA) and from mouse models of the disease, to identify Lasp1 as an epigenomically co-modified region in chronic inflammatory arthritis and a functionally important binding partner of the Cadherin-11/β-Catenin complex in zipper-like cell-to-cell contacts. In vitro, loss or blocking of Lasp1 alters pathological tissue formation, migratory behaviour and platelet-derived growth factor response of arthritic FLS. In arthritic human TNF transgenic mice, deletion of Lasp1 reduces arthritic joint destruction. Therefore, we show a function of Lasp1 in cellular junction formation and inflammatory tissue remodelling and identify Lasp1 as a potential target for treating inflammatory joint disorders associated with aggressive cellular transformation.*

Pro-inflammatory immunity supports fibrosis advancement in epidermolysis bullosa: intervention with Ang-(1-7). Bernasconi R, Thriene K, Romero-Fernández E, Gretzmeier C, Kühl T, Maler M, Nauroy P, Kleiser S, Rühl-Muth AC, Stumpe M, Kiritsi D, Martin SF, Hinz B, Bruckner-Tuderman L, Dengjel J, Nyström A. EMBO Mol Med. 2021 Aug 30:e14392. doi: 10.15252/emmm.202114392.
Corresponding author: alexander.nystroem@uniklinik-freiburg.de
Abstract: *Recessive dystrophic epidermolysis bullosa (RDEB), a genetic skin blistering disease, is a paradigmatic condition of tissue fragility-driven multi-organ fibrosis. Here, longitudinal analyses of the tissue proteome through the course of naturally developing disease in RDEB mice revealed that increased pro-inflammatory immunity associates with fibrosis evolution. Mechanistically, this fibrosis is a consequence of altered extracellular matrix organization rather than that of increased abundance of major structural proteins. In a humanized system of disease progression, we targeted inflammatory cell fibroblast communication with Ang-(1-7)-an anti-inflammatory heptapeptide of the renin-angiotensin system, which reduced the fibrosis-evoking aptitude of RDEB cells. In vivo, systemic administration of Ang-(1-7) efficiently attenuated progression of multi-organ fibrosis and*

increased survival of RDEB mice. Collectively, our study shows that selective down-modulation of pro-inflammatory immunity may mitigate injury-induced fibrosis. Furthermore, together with published data, our data highlight molecular diversity among fibrotic conditions. Both findings have direct implications for the design of therapies addressing skin fragility and fibrosis.

Mitochondrial respiratory chain function promotes extracellular matrix integrity in cartilage. Bubb K, Holzer T, Nolte JL, Krüger M, Wilson R, Schlötzer-Schrehardt U, Brinckmann J, Altmüller J, Aszodi A, Fleischhauer L, Clausen-Schaumann H, Probst K, Brachvogel B. J Biol Chem. 2021 Sep 21:101224. doi: 10.1016/j.jbc.2021.101224.
Corresponding author: bent.brachvogel@uni-koeln.de
Abstract: *Energy metabolism and extracellular matrix function together orchestrate and maintain tissue organization, but crosstalk between these processes is poorly understood. Here, we used single cell RNA-seq (scRNA-seq) analysis to uncover the importance of the mitochondrial respiratory chain for extracellular matrix homeostasis in mature cartilage. This tissue produces large amounts of a specialized extracellular matrix to promote skeletal growth during development and maintain mobility throughout life. A combined approach of high-resolution scRNA-seq, mass spectrometry/matrisome analysis, and atomic force microscopy was applied to mutant mice with cartilage-specific inactivation of respiratory chain function. This genetic inhibition in cartilage results in the expansion of a central area of 1-month-old mouse femur head cartilage, showing disorganized chondrocytes and increased deposition of extracellular matrix material. scRNA-seq analysis identified a cell cluster-specific decrease in mitochondrial DNA-encoded respiratory chain genes and a unique regulation of extracellular matrix-related genes in nonarticular chondrocytes. These changes were associated with alterations in extracellular matrix composition, a shift in collagen/non-collagen protein content, and an increase of collagen crosslinking and ECM stiffness. These results demonstrate that mitochondrial respiratory chain dysfunction is a key factor that can promote ECM integrity and mechanostability in cartilage and presumably also in many other tissues.*

BMP antagonists in tissue development and disease. Correns A, Zimmermann LA, Baldock C, Sengle G. Matrix Biol Plus. 2021 Jun 11;11:100071. doi: 10.1016/j.mbplus.2021.100071.
Corresponding author: gsengle@uni-koeln.de
Abstract: *Bone morphogenic proteins (BMPs) are important growth regulators in embryogenesis and postnatal homeostasis. Their tight regulation is crucial for successful embryonic development as well as tissue homeostasis in the adult organism. BMP inhibition by natural extracellular biologic antagonists represents the most intensively studied mechanistic concept of BMP growth factor regulation. It was shown to be critical for numerous developmental programs, including germ layer specification and spatiotemporal gradients required for the establishment of the dorsal-ventral axis and organ formation. The importance of BMP antagonists for extracellular matrix homeostasis is illustrated by the numerous human connective tissue disorders caused by their mutational inactivation. Here, we will focus on the known functional interactions targeting BMP antagonists to the ECM and discuss how these interactions influence BMP antagonist activity. Moreover, we will provide an overview about the current concepts and investigated molecular mechanisms modulating BMP inhibitor function in the context of development and disease.*

The Role of microRNA Let-7d in Female Malignancies and Diseases of the Female Reproductive Tract. De Santis C, Götte M. Int J Mol Sci. 2021 Jul 8;22(14):7359. doi: 10.3390/ijms22147359.
Corresponding author: martingotte@uni-muenster.de
Abstract: *microRNAs are small noncoding RNAs that regulate gene expression at the posttranscriptional level. Let-7d is a microRNA of the conserved let-7 family that is dysregulated in female malignancies including breast cancer, ovarian cancer, endometrial cancer, and cervical cancer. Moreover, a dysregulation is observed in endometriosis*

and pregnancy-associated diseases such as preeclampsia and fetal growth restriction. Let-7d expression is regulated by cytokines and steroids, involving transcriptional regulation by OCT4, MYC and p53, as well as posttranscriptional regulation via LIN28 and ADAR. By downregulating a wide range of relevant mRNA targets, let-7d affects cellular processes that drive disease progression such as cell proliferation, apoptosis (resistance), angiogenesis and immune cell function. In an oncological context, let-7d has a tumor-suppressive function, although some of its functions are context-dependent. Notably, its expression is associated with improved therapeutic responses to chemotherapy in breast and ovarian cancer. Studies in mouse models have furthermore revealed important roles in uterine development and function, with implications for obstetric diseases. Apart from a possible utility as a diagnostic blood-based biomarker, pharmacological modulation of let-7d emerges as a promising therapeutic concept in a variety of female disease conditions.

Pathogenic variants in GNPTAB and GNPTG encoding distinct subunits of GlcNAc-1-phosphotransferase differentially impact bone resorption in patients with mucolipidosis type II and III. Di Lorenzo G, Westermann LM, Yorgan TA, Stürznickel J, Ludwig NF, Ammer LS, Baranowsky A, Ahmadi S, Pourbarkhordariesfandabadi E, Breyer SR, Board TN, Foster A, Mercer J, Tylee K, Velho RV, Schweizer M, Renné T, Braulke T, Randon DN, Sperb-Ludwig F, de Camargo Pinto LL, Moreno CA, Cavalcanti DP, Amling M, Kutsche K, Winter D, Muschol NM, Schwartz IVD, Rolvien T, Danyukova T, Schinke T, Pohl S. Genet Med. 2021 Aug 2. doi: 10.1038/s41436-021-01285-9.
Corresponding author: s.pohl@uke.de
Abstract: Purpose: *Pathogenic variants in GNPTAB and GNPTG, encoding different subunits of GlcNAc-1-phosphotransferase, cause mucolipidosis (ML) II, MLIII alpha/beta, and MLIII gamma. This study aimed to investigate the cellular and molecular bases underlying skeletal abnormalities in patients with MLII and MLIII.* ***Methods:*** *We analyzed bone biopsies from patients with MLIII alpha/beta or MLIII gamma by undecalcified histology and histomorphometry. The skeletal status of Gnptg^{ko} and Gnptab-deficient mice was determined and complemented by biochemical analysis of primary Gnptg^{ko} bone cells. The clinical relevance of the mouse data was underscored by systematic urinary collagen crosslinks quantification in patients with MLII, MLIII alpha/beta, and MLIII gamma.* ***Results:*** *The analysis of iliac crest biopsies revealed that bone remodeling is impaired in patients with GNPTAB-associated MLIII alpha/beta but not with GNPTG-associated MLIII gamma. Opposed to Gnptab-deficient mice, skeletal remodeling is not affected in Gnptg^{ko} mice. Most importantly, patients with variants in GNPTAB but not in GNPTG exhibited increased bone resorption.* ***Conclusion:*** *The gene-specific impact on bone remodeling in human individuals and in mice proposes distinct molecular functions of the GlcNAc-1-phosphotransferase subunits in bone cells. We therefore appeal for the necessity to classify MLIII based on genetic in addition to clinical criteria to ensure appropriate therapy.*

Dispatching plasma membrane cholesterol and Sonic Hedgehog dispatch: two sides of the same coin? Ehring K, Grobe K. Biochem Soc Trans. 2021 Sep 13:BST20210918. doi: 10.1042/BST20210918.
Corresponding author: kgrobe@uni-muenster.de
Abstract: *Vertebrate and invertebrate Hedgehog (Hh) morphogens signal over short and long distances to direct cell fate decisions during development and to maintain tissue homeostasis after birth. One of the most important questions in Hh biology is how such Hh signaling to distant target cells is achieved, because all Hh proteins are secreted as dually lipidated proteins that firmly tether to the outer plasma membrane leaflet of their producing cells. There, Hhs multimerize into light microscopically visible storage platforms that recruit factors required for their regulated release. One such recruited release factor is the soluble glycoprotein Scube2 (Signal sequence, cubulin domain, epidermal-growth-factor-like protein 2), and maximal Scube2 function requires concomitant activity of the resistance-nodulation-division (RND) transporter Dispatched (Disp) at the plasma membrane of Hh-producing cells. Although recently published cryo-electron microscopy-derived structures suggest possible direct modes of Scube2/Disp-regulated Hh release, the mechanism of Disp-mediated Hh deployment is still not fully*

understood. In this review, we discuss suggested direct modes of Disp-dependent Hh deployment and relate them to the structural similarities between Disp and the related RND transporters Patched (Ptc) and Niemann-Pick type C protein 1. We then discuss open questions and perspectives that derive from these structural similarities, with particular focus on new findings that suggest shared small molecule transporter functions of Disp to deplete the plasma membrane of cholesterol and to modulate Hh release in an indirect manner.

Conserved cholesterol-related activities of Dispatched 1 drive Sonic hedgehog shedding from the cell membrane. Ehring K, Manikowski D, Goretzko J, Froese J, Gude F, Jakobs P, Rescher U, Kirchhefer U, Grobe K. J Cell Sci. 2022 Mar 1;135(5):jcs258672. doi: 10.1242/jcs.258672.
Corresponding author: kgrobe@uni-muenster.de
Abstract: *The Sonic hedgehog (Shh) pathway controls embryonic development and tissue homeostasis after birth. Long-standing questions about this pathway include how the dual-lipidated, firmly plasma membrane-associated Shh ligand is released from producing cells to signal to distant target cells and how the resistance-nodulation-division transporter Dispatched 1 (Disp, also known as Disp1) regulates this process. Here, we show that inactivation of Disp in Shh-expressing human cells impairs proteolytic Shh release from its lipidated terminal peptides, a process called ectodomain shedding. We also show that cholesterol export from Disp-deficient cells is reduced, that these cells contain increased cholesterol amounts in the plasma membrane, and that Shh shedding from Disp-deficient cells is restored by pharmacological membrane cholesterol extraction and by overexpression of transgenic Disp or the structurally related protein Patched 1 (Ptc, also known as Ptch1; a putative cholesterol transporter). These data suggest that Disp can regulate Shh function via controlled cell surface shedding and that membrane cholesterol-related molecular mechanisms shared by Disp and Ptc exercise such sheddase control.*

Metabolic orchestration of the wound healing response. Eming SA, Murray PJ, Pearce EJ. Cell Metab. 2021 Sep 7;33(9):1726-1743. doi: 10.1016/j.cmet.2021.07.017.
Corresponding author: sabine.eming@uni-koeln.de and murray@biochem.mpg.de and epearce7@jhmi.edu
Abstract: *Wound healing requires cooperation between different cell types, among which macrophages play a central role. In particular, inflammatory macrophages are engaged in the initial response to wounding, and alternatively activated macrophages are essential for wound closure and the resolution of tissue repair. The links between temporal activation-induced changes in the metabolism of such macrophages and the influence this has on their functional states, along with the realization that metabolites play both intrinsic and extrinsic roles in the cells that produce them, has focused attention on the metabolism of wound healing. Here, we discuss macrophage metabolism during distinct stages of normal healing and its related pathologic processes, such as during cancer and fibrosis. Further, we frame these insights in a broader context of the current understanding of macrophage metabolic reprogramming linked to cellular activation and function. Finally, we discuss parallels between the metabolism of macrophages and fibroblasts, the latter being a key stromal cell type in wound healing, and consider the importance of the metabolic interplay between different cell types in the wound microenvironment.*
Heparan Sulfate Deficiency in Cartilage: Enhanced BMP-Sensitivity, Proteoglycan Production and an Anti-Apoptotic Expression Signature after Loading. Gerstner M, Severmann AC, Chasan S, Vortkamp A, Richter W. Int J Mol Sci. 2021 Apr 2;22(7):3726. doi: 10.3390/ijms22073726.
Corresponding author: wiltrud.richter@med.uni-heidelberg.de
Abstract: *Osteoarthritis (OA) represents one major cause of disability worldwide still evading efficient pharmacological or cellular therapies. Severe degeneration of extracellular cartilage matrix precedes the loss of mobility and disabling pain perception in affected joints. Recent studies showed that a reduced heparan sulfate (HS) content protects cartilage from degradation in OA-animal models of joint destabilization but the underlying mechanisms remained unclear. We aimed to clarify whether low HS-content alters the mechano-response of chondrocytes and to uncover pathways relevant for HS-related chondro-protection in response to loading. Tissue-*

engineered cartilage with HS-deficiency was generated from rib chondrocytes of mice carrying a hypomorphic allele of Exostosin 1 (Ext1), one of the main HS-synthesizing enzymes, and wildtype (WT) littermate controls. Engineered cartilage matured for 2 weeks was exposed to cyclic unconfined compression in a bioreactor. The molecular loading response was determined by transcriptome profiling, bioinformatic data processing, and qPCR. HS-deficient chondrocytes expressed 3-6% of WT Ext1-mRNA levels. Both groups similarly raised Sox9, Col2a1 and Acan levels during maturation. However, HS-deficient chondrocytes synthesized and deposited 50% more GAG/DNA. TGFβ and FGF2-sensitivity of $Ext1^{gt/gt}$ chondrocytes was similar to WT cells but their response to BMP-stimulation was enhanced. Loading induced similar activation of mechano-sensitive ERK and P38-signaling in WT and HS-reduced chondrocytes. Transcriptome analysis reflected regulation of cell migration as major load-induced biological process with similar stimulation of common (Fosl1, Itgα5, Timp1, and Ngf) as well as novel mechano-regulated genes (Inhba and Dhrs9). Remarkably, only Ext1-hypomorphic cartilage responded to loading by an expression signature of negative regulation of apoptosis with pro-apoptotic Bnip3 being selectively down-regulated. HS-deficiency enhanced BMP-sensitivity, GAG-production and fostered an anti-apoptotic expression signature after loading, all of which may protect cartilage from load-induced erosion.

Osteoarthritis: Novel Molecular Mechanisms Increase Our Understanding of the Disease Pathology. Grässel S, Zaucke F, Madry H. J Clin Med. 2021 Apr 30;10(9):1938. doi: 10.3390/jcm10091938.
Corresponding author: susanne.graessel@ukr.de
Abstract: *Although osteoarthritis (OA) is the most common musculoskeletal condition that causes significant health and social problems worldwide, its exact etiology is still unclear. With an aging and increasingly obese population, OA is becoming even more prevalent than in previous decades. Up to 35% of the world's population over 60 years of age suffers from symptomatic (painful, disabling) OA. The disease poses a tremendous economic burden on the health-care system and society for diagnosis, treatment, sick leave, rehabilitation, and early retirement. Most patients also experience sleep disturbances, reduced capability for exercising, lifting, and walking and are less capable of working, and maintaining an independent lifestyle. For patients, the major problem is disability, resulting from joint tissue destruction and pain. So far, there is no therapy available that effectively arrests structural deterioration of cartilage and bone or is able to successfully reverse any of the existing structural defects. Here, we elucidate novel concepts and hypotheses regarding disease progression and pathology, which are relevant for understanding underlying the molecular mechanisms as a prerequisite for future therapeutic approaches. Emphasis is placed on topographical modeling of the disease, the role* of proteases and cytokines in OA, and the impact of the peripheral nervous system and its neuropeptides.

Macrophage-Mediated Tissue Vascularization: Similarities and Differences Between Cornea and Skin. Hadrian K, Willenborg S, Bock F, Cursiefen C, Eming SA, Hos D. Front Immunol. 2021 Apr 7;12:667830. doi: 10.3389/fimmu.2021.667830.
Corresponding author: sabine.eming@uni-koeln.de and deniz.hos@uk-koeln.de
Abstract: *Macrophages are critical mediators of tissue vascularization both in health and disease. In multiple tissues, macrophages have been identified as important regulators of both blood and lymphatic vessel growth, specifically following tissue injury and in pathological inflammatory responses. In development, macrophages have also been implicated in limiting vascular growth. Hence, macrophages provide an important therapeutic target to modulate tissue vascularization in the clinic. However, the molecular mechanisms how macrophages mediate tissue vascularization are still not entirely resolved. Furthermore, mechanisms might also vary among different tissues. Here we review the role of macrophages in tissue vascularization with a focus on their role in blood and lymphatic vessel formation in the barrier tissues cornea and skin. Comparing mechanisms of macrophage-mediated hem- and lymphangiogenesis in the angiogenically privileged cornea and the physiologically vascularized skin provides an opportunity to highlight similarities but also tissue-specific*

differences, and to understand how macrophage-mediated hem- and lymphangiogenesis can be exploited for the treatment of disease, including corneal wound healing after injury, graft rejection after corneal transplantation or pathological vascularization of the skin.

Loss of sphingosine kinase 2 enhances Wilm's tumor suppressor gene 1 and nephrin expression in podocytes and protects from streptozotocin-induced podocytopathy and albuminuria in mice. Imeri F, Stepanovska Tanturovska B, Schwalm S, Saha S, Zeng-Brouwers J, Pavenstädt H, Pfeilschifter J, Schaefer L, Huwiler A. Matrix Biol. 2021 Apr;98:32-48. doi: 10.1016/j.matbio.2021.05.003.
Corresponding author: schaefer@med.uni-frankfurt.de and huwiler@pki.unibe.ch
Abstract: *The sphingosine 1-phosphate (S1P) is a bioactive sphingolipid that is now appreciated as key regulatory factor for various cellular functions in the kidney, including matrix remodeling. It is generated by two sphingosine kinases (Sphk), Sphk1 and Sphk2, which are ubiquitously expressed, but have distinct enzymatic activities and subcellular localizations. In this study, we have investigated the role of Sphk2 in podocyte function and its contribution to diabetic nephropathy. We show that streptozotocin (STZ)-induced nephropathy and albuminuria in mice is prevented by genetic depletion of Sphk2. This protection correlated with an increased protein expression of the transcription factor Wilm's tumor suppressor gene 1 (WT1) and its target gene nephrin, and a reduced macrophage infiltration in immunohistochemical renal sections of STZ-treated Sphk2$^{-/-}$ mice compared to STZ-treated wildtype mice. To investigate changes on the cellular level, we used an immortalized human podocyte cell line and generated a stable knockdown of Sphk2 (Sphk2-kd) by a lentiviral transduction method. These Sphk2-kd cells accumulated sphingosine as a consequence of the knockdown, and showed enhanced nephrin and WT1 mRNA and protein expressions similar to the finding in Sphk2 knockout mice. Treatment of wildtype podocytes with the highly selective Sphk2 inhibitor SLM6031434 caused a similar upregulation of nephrin and WT1 expression. Furthermore, exposing cells to the profibrotic mediator transforming growth factor β (TGFβ) resulted on the one side in reduced nephrin and WT1 expression, but on the other side, in upregulation of various profibrotic marker proteins, including connective tissue growth factor (CTGF), fibronectin (FN) and plasminogen activator inhibitor (PAI) 1. All these effects were reverted by Sphk2-kd and SLM6031434. Mechanistically, the protection by Sphk2-kd may depend on accumulated sphingosine and inhibited PKC activity, since treatment of cells with exogenous sphingosine not only reduced the phosphorylation pattern of PKC substrates, but also increased WT1 protein expression. Moreover, the selective stable knockdown of PKCδ increased WT1 expression, suggesting the involvement of this PKC isoenzyme in WT1 regulation. The glucocorticoid dexamethasone, which is a treatment option in many glomerular diseases and is known to mediate a nephroprotection, not only downregulated Sphk2 and enhanced cellular sphingosine, but also enhanced WT1 and nephrin expressions, thus, suggesting that parts of the nephroprotective effect of dexamethasone is mediated by Sphk2 downregulation. Altogether, our data demonstrated that loss of Sphk2 is protective in diabetes-induced podocytopathy and can prevent proteinuria, which is a hallmark of many glomerular diseases. Thus, Sphk2 could serve as a new attractive pharmacological target to treat proteinuric kidney diseases.*

Identification and characterisation of tertiary lymphoid organs in human type 1 diabetes. Korpos É, Kadri N, Loismann S, Findeisen CR, Arfuso F, Burke GW 3rd, Richardson SJ, Morgan NG, Bogdani M, Pugliese A, Sorokin L. Diabetologia. 2021 Jul;64(7):1626-1641. doi: 10.1007/s00125-021-05453-z.
Corresponding author: korpos@uni-muenster.de
Abstract*: **Aims/hypothesis:** We and others previously reported the presence of tertiary lymphoid organs (TLOs) in the pancreas of NOD mice, where they play a role in the development of type 1 diabetes. Our aims here are to investigate whether TLOs are present in the pancreas of individuals with type 1 diabetes and to characterise their distinctive features, in comparison with TLOs present in NOD mouse pancreases, in order to interpret their functional significance. **Methods:** Using immunofluorescence confocal microscopy, we examined the extracellular*

matrix (ECM) and cellular constituents of pancreatic TLOs from individuals with ongoing islet autoimmunity in three distinct clinical settings of type 1 diabetes: at risk of diabetes; at/after diagnosis; and in the transplanted pancreas with recurrent diabetes. Comparisons were made with TLOs from 14-week-old NOD mice, which contain islets exhibiting mild to heavy leucocyte infiltration. We determined the frequency of the TLOs in human type 1diabetes with insulitis and investigated the presence of TLOs in relation to age of onset, disease duration and disease severity. ***Results:*** *TLOs were identified in preclinical and clinical settings of human type 1 diabetes. The main characteristics of these TLOs, including the cellular and ECM composition of reticular fibres (RFs), the presence of high endothelial venules and immune cell subtypes detected, were similar to those observed for TLOs from NOD mouse pancreases. Among 21 donors with clinical type 1 diabetes who exhibited insulitis, 12 had TLOs and had developed disease at younger age compared with those lacking TLOs. Compartmentalised TLOs with distinct T cell and B cell zones were detected in donors with short disease duration. Overall, TLOs were mainly associated with insulin-containing islets and their frequency decreased with increasing severity of beta cell loss. Parallel studies in NOD mice further revealed some differences in so far as regulatory T cells were essentially absent from human pancreatic TLOs and CCL21 was not associated with RFs.* ***Conclusions/interpretation:*** *We demonstrate a novel feature of pancreas pathology in type 1 diabetes. TLOs represent a potential site of autoreactive effector T cell generation in islet autoimmunity and our data from mouse and human tissues suggest that they disappear once the destructive process has run its course. Thus, TLOs may be important for type 1 diabetes progression.*

Distinct contributions of meprins to skin regeneration after injury - Meprin α a physiological processer of pro-collagen VII. Kruppa D, Peters F, Bornert O, Maler MD, Martin SF, Becker-Pauly C, Nyström A. Matrix Biol Plus. 2021 May 13;11:100065. doi: 10.1016/j.mbplus.2021.100065.
Corresponding author: alexander.nystroem@uniklinik-freiburg.de
Abstract: *Astacin-like proteinases (ALPs) are regulators of tissue and extracellular matrix (ECM) homeostasis. They convey this property through their ability to convert ECM protein pro-forms to functional mature proteins and by regulating the bioavailability of growth factors that stimulate ECM synthesis. The most studied ALPs in this context are the BMP-1/tolloid-like proteinases. The other subclass of ALPs in vertebrates - the meprins, comprised of meprin α and meprin β - are emerging as regulators of tissue and ECM homeostasis but have so far been only limitedly investigated. Here, we functionally assessed the roles of meprins in skin wound healing using mice genetically deficient in one or both meprins. Meprin deficiency did not change the course of macroscopic wound closure. However, subtle but distinct contributions of meprins to the healing process and dermal homeostasis were observed. Loss of both meprins delayed re-epithelialization and reduced macrophage infiltration. Abnormal dermal healing and ECM regeneration was observed in meprin deficient wounds. Our analyses also revealed meprin α as one proteinase responsible for maturation of pro-collagen VII to anchoring fibril-forming-competent collagen VII in vivo. Collectively, our study identifies meprins as subtle players in skin wound healing.*

Curcumin-primed human BMSC-derived extracellular vesicles reverse IL-1β-induced catabolic responses of OA chondrocytes by upregulating miR-126-3p. Li S, Stöckl S, Lukas C, Herrmann M, Brochhausen C, König MA, Johnstone B, Grässel S. Stem Cell Res Ther. 2021 Apr 29;12(1):252. doi: 10.1186/s13287-021-02317-6.
Corresponding author: susanne.graessel@ukr.de
Abstract: ***Background:*** *Curcumin has anti-inflammatory effects and qualifies as a potential candidate for the treatment of osteoarthritis (OA). However, curcumin has limited bioavailability. Extracellular vesicles (EVs) are released by multiple cell types and act as molecule carrier during intercellular communication. We assume that EVs can maintain bioavailability and stability of curcumin after encapsulation. Here, we evaluated modulatory effects of curcumin-primed human (h)BMSC-derived EVs (Cur-EVs) on IL-1β stimulated human osteoarthritic chondrocytes (OA-CH).* ***Methods:*** *CellTiter-Blue Viability- (CTB), Caspase 3/7-, and live/dead assays were used to*

determine range of cytotoxic curcumin concentrations for hBMSC and OA-CH. Cur-EVs and control EVs were harvested from cell culture supernatants of hBMSC by ultracentrifugation. Western blotting (WB), transmission electron microscopy, and nanoparticle tracking analysis were performed to characterize the EVs. The intracellular incorporation of EVs derived from PHK26 labeled and curcumin-primed or control hBMSC was tested by adding the labeled EVs to OA-CH cultures. OA-CH were pre-stimulated with IL-1β, followed by Cur-EV and control EV treatment for 24 h and subsequent analysis of viability, apoptosis, and migration (scratch assay). Relative expression of selected anabolic and catabolic genes was assessed with qRT-PCR. Furthermore, WB was performed to evaluate phosphorylation of Erk1/2, PI3K/Akt, and p38MAPK in OA-CH. The effect of hsa-miR-126-3p expression on IL-1β-induced OA-CH was determined using CTB-, Caspase 3/7-, live/dead assays, and WB. ***Results:*** *Cur-EVs promoted viability and reduced apoptosis of IL-1β-stimulated OA-CH and attenuated IL-1β-induced inhibition of migration. Furthermore, Cur-EVs increased gene expression of BCL2, ACAN, SOX9, and COL2A1 and decreased gene expression of IL1B, IL6, MMP13, and COL10A1 in IL-1β-stimulated OA-CH. In addition, phosphorylation of Erk1/2, PI3K/Akt, and p38 MAPK, induced by IL-1β, is prevented by Cur-EVs. Cur-EVs increased IL-1β-reduced expression of hsa-miR-126-3p and hsa-miR-126-3p mimic reversed the effects of IL-1β.* ***Conclusion:*** *Cur-EVs alleviated IL-1β-induced catabolic effects on OA-CH by promoting viability and migration, reducing apoptosis and phosphorylation of Erk1/2, PI3K/Akt, and p38 MAPK thereby modulating pro-inflammatory signaling pathways. Treatment of OA-CH with Cur-EVs is followed by upregulation of expression of hsa-miR-126-3p which is involved in modulation of anabolic response of OA-CH. EVs may be considered as promising drug delivery vehicles of curcumin helping to alleviate OA.*

Expression and Localization of Thrombospondins, Plastin 3, and STIM1 in Different Cartilage Compartments of the Osteoarthritic Varus Knee. Mählich D, Glasmacher A, Müller I, Oppermann J, Grevenstein D, Eysel P, Heilig J, Wirth B, Zaucke F, Niehoff A. Int J Mol Sci. 2021 Mar 17;22(6):3073. doi: 10.3390/ijms22063073.
Corresponding author: niehoff@dshs-koeln.de
Abstract: *Osteoarthritis (OA) is a multifactorial disease which is characterized by a change in the homeostasis of the extracellular matrix (ECM). The ECM is essential for the function of the articular cartilage and plays an important role in cartilage mechanotransduction. To provide a better understanding of the interaction between the ECM and the actin cytoskeleton, we investigated the localization and expression of the Ca^{2+}-dependent proteins cartilage oligomeric matrix protein (COMP), thrombospondin-1 (TSP-1), plastin 3 (PLS3) and stromal interaction molecule 1 (STIM1). We investigated 16 patients who suffered from varus knee OA and performed a topographical analysis of the cartilage from the medial and lateral compartment of the proximal tibial plateau. In a varus knee, OA is more pronounced in the medial compared to the lateral compartment as a result of an overloading due to the malalignment. We detected a location-dependent staining of PLS3 and STIM1 in the articular cartilage tissue. The staining intensity for both proteins correlated with the degree of cartilage degeneration. The staining intensity of TSP-1 was clearly reduced in the cartilage of the more affected medial compartment, an observation that was confirmed in cartilage extracts by immunoblotting. The total amount of COMP was unchanged; however, slight changes were detected in the localization of the protein. Our results provide novel information on alterations in OA cartilage suggesting that Ca^{2+}-dependent mechanotransduction between the ECM and the actin cytoskeleton might play an essential role in the pathomechanism of OA.*

Syndecan-1 Promotes Angiogenesis in Triple-Negative Breast Cancer through the Prognostically Relevant Tissue Factor Pathway and Additional Angiogenic Routes. Nassar E, Hassan N, El-Ghonaimy EA, Hassan H, Abdullah MS, Rottke TV, Kiesel L, Greve B, Ibrahim SA, Götte M. Cancers (Basel). 2021 May 12;13(10):2318. doi: 10.3390/cancers13102318.
Corresponding author: martingotte@uni-muenster.de and isherif@sci.cu.edu.eg

Abstract: *Triple-negative breast cancer (TNBC) is characterized by increased angiogenesis, metastasis, and poor survival. Dysregulation of the cell surface heparan sulfate proteoglycan and signaling co-receptor Syndecan-1 is linked to poor prognosis. To study its role in angiogenesis, we silenced Syndecan-1 in TNBC cell lines using a 3D human umbilical vein endothelial cell (HUVEC) co-culture system. Syndecan-1 siRNA depletion in SUM-149, MDA-MB-468, and MDA-MB-231 cells decreased HUVEC tubule network formation. Angiogenesis array revealed reduced VEGF-A and tissue factor (TF) in the Syndecan-1-silenced secretome. qPCR independently confirmed altered expression of F3, F7, F2R/PAR1, F2RL1/PAR2, VEGF-A, EDN1, IGFBP1, and IGFBP2 in SUM-149, MDA-MB-231, and MDA-MB-468 cells. ELISA revealed reduced secreted endothelin-1 (SUM-149, MDA-MB-468) and TF (all cell lines) upon Syndecan-1 depletion, while TF pathway inhibitor treatment impaired angiogenesis. Survival analysis of 3951 patients demonstrated that high expression of F3 and F7 are associated with better relapse-free survival, whereas poor survival was observed in TNBC and p53 mutant basal breast cancer (F3) and in ER-negative and HER2-positive breast cancer (F2R, F2RL1). STRING protein network analysis revealed associations of Syndecan-1 with VEGF-A and IGFBP1, further associated with the TF and ET-1 pathways. Our study suggests that TNBC Syndecan-1 regulates angiogenesis via the TF and additional angiogenic pathways and marks its constituents as novel prognostic markers and therapeutic targets.*

An mTORC1-GRASP55 signaling axis controls unconventional secretion to reshape the extracellular proteome upon stress. Nüchel J, Tauber M, Nolte JL, Mörgelin M, Türk C, Eckes B, Demetriades C, Plomann M. Mol Cell. 2021 Aug 19;81(16):3275-3293.e12. doi: 10.1016/j.molcel.2021.06.017.

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Abstract: *Cells communicate with their environment via surface proteins and secreted factors. Unconventional protein secretion (UPS) is an evolutionarily conserved process, via which distinct cargo proteins are secreted upon stress. Most UPS types depend upon the Golgi-associated GRASP55 protein. However, its regulation and biological role remain poorly understood. Here, we show that the mechanistic target of rapamycin complex 1 (mTORC1) directly phosphorylates GRASP55 to maintain its Golgi localization, thus revealing a physiological role for mTORC1 at this organelle. Stimuli that inhibit mTORC1 cause GRASP55 dephosphorylation and relocalization to UPS compartments. Through multiple, unbiased, proteomic analyses, we identify numerous cargoes that follow this unconventional secretory route to reshape the cellular secretome and surfactome. Using MMP2 secretion as a proxy for UPS, we provide important insights on its regulation and physiological role. Collectively, our findings reveal the mTORC1-GRASP55 signaling hub as the integration point in stress signaling upstream of UPS and as a key coordinator of the cellular adaptation to stress.*

Platelets, Constant and Cooperative Companions of Sessile and Disseminating Tumor Cells, Crucially Contribute to the Tumor Microenvironment. Obermann WMJ, Brockhaus K, Eble JA. Front Cell Dev Biol. 2021 Apr 16;9:674553. doi: 10.3389/fcell.2021.674553.

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Abstract: *Although platelets and the coagulation factors are components of the blood system, they become part of and contribute to the tumor microenvironment (TME) not only within a solid tumor mass, but also within a hematogenous micrometastasis on its way through the blood stream to the metastatic niche. The latter basically consists of blood-borne cancer cells which are in close association with platelets. At the site of the primary tumor, the blood components reach the TME via leaky blood vessels, whose permeability is increased by tumor-secreted growth factors, by incomplete angiogenic sprouts or by vasculogenic mimicry (VM) vessels. As a consequence, platelets reach the primary tumor via several cell adhesion molecules (CAMs). Moreover, clotting factor VII from the blood associates with tissue factor (TF) that is abundantly expressed on cancer cells. This extrinsic tenase complex turns on the coagulation cascade, which encompasses the activation of thrombin and conversion of soluble fibrinogen into insoluble fibrin. The presence of platelets and their release of growth factors, as well as*

fibrin deposition changes the TME of a solid tumor mass substantially, thereby promoting tumor progression. Disseminating cancer cells that circulate in the blood stream also recruit platelets, primarily by direct cell-cell interactions via different receptor-counterreceptor pairs and indirectly by fibrin, which bridges the two cell types via different integrin receptors. These tumor cell-platelet aggregates are hematogenous micrometastases, in which platelets and fibrin constitute a particular TME in favor of the cancer cells. Even at the distant site of settlement, the accompanying platelets help the tumor cell to attach and to grow into metastases. Understanding the close liaison of cancer cells with platelets and coagulation factors that change the TME during tumor progression and spreading will help to curb different steps of the metastatic cascade and may help to reduce tumor-induced thrombosis.

microRNA-140-3p modulates invasiveness, motility, and extracellular matrix adhesion of breast cancer cells by targeting syndecan-4. Onyeisi JOS, Greve B, Espinoza-Sánchez NA, Kiesel L, Lopes CC, Götte M. J Cell Biochem. 2021 Oct;122(10):1491-1505. doi: 10.1002/jcb.30071.
Corresponding author: martingotte@uni-muenster.de and jessicaoyie@hotmail.com
Abstract: *Syndecan-4, a predicted target of the microRNA miR-140-3p, plays an important role in multiple steps of tumor progression and is the second most abundant heparan sulfate proteoglycan produced by breast carcinoma cell lines. To investigate the potential functional relationship of miR-140-3p and syndecan-4, MDA-MB-231, SKBR3, and MCF-7 breast cancer (BC) cells were transiently transfected with pre-miR-140-3p, syndecan-4 small interfering RNAJ, or control reagents, respectively. Altered cell behavior was monitored by adhesion, migration, and invasion chamber assays. Moreover, the prognostic value of syndecan-4 was assessed by Kaplan-Maier Plotter analysis of gene expression data from tumor samples of 4929 patients. High expression of syndecan-4 was associated with better relapse-free survival in the whole collective of BC patients, but correlated with a worse survival in the subgroup of estrogen receptor negative and estrogen/progesterone-receptor negative patients. miR-140-3p expression was associated with improved survival irrespective of hormone receptor status. miR-140-3p overexpression induced posttranscriptional downregulation of syndecan-4, as demonstrated by quantitative real-time PCR (qPCR), flow cytometry, and luciferase assays, resulting in decreased BC cell migration and matrigel invasiveness. Furthermore, miR-140-3p overexpression and syndecan-4 silencing increased the adhesion of BC to fibronectin and laminin. qPCR analysis demonstrated that syndecan-4 silencing leads to altered gene expression of adhesion-related molecules, such as fibronectin and focal adhesion kinase, as well as in the gene expression of the proinvasive factors matrix metalloproteinase 2 and heparanase (also known as HPSE). We conclude that syndecan-4 is a novel target of miR*-140-3p that regulates BC cell invasiveness and cell-matrix interactions in the tumor microenvironment.

Fibroblast MMP14-Dependent Collagen Processing Is Necessary for Melanoma Growth. Pach E, Brinckmann J, Rübsam M, Kümper M, Mauch C, Zigrino P. Cancers (Basel). 2021 Apr 20;13(8):1984. doi: 10.3390/cancers13081984.
Corresponding author: paola.zigrino@uni-koeln.de
Abstract: *Skin homeostasis results from balanced synthesis and degradation of the extracellular matrix in the dermis. Deletion of the proteolytic enzyme MMP14 in dermal fibroblasts (MMP14$^{Sf-/-}$) leads to a fibrotic skin phenotype with the accumulation of collagen type I, resulting from impaired proteolysis. Here, we show that melanoma growth in these mouse fibrotic dermal samples was decreased, paralleled by reduced tumor cell proliferation and vessel density. Using atomic force microscopy, we found increased peritumoral matrix stiffness of early but not late melanomas in the absence of fibroblast-derived MMP14. However, total collagen levels were increased at late melanoma stages in MMP14$^{Sf-/-}$ mice compared to controls. In ex vivo invasion assays, melanoma cells formed smaller tumor islands in MMP14$^{Sf-/-}$ skin, indicating that MMP14-dependent matrix accumulation regulates tumor growth. In line with these data, in vitro melanoma cell growth was inhibited in high collagen 3D*

spheroids or stiff substrates. Most importantly, in vivo induction of fibrosis using bleomycin reduced melanoma tumor growth. In summary, we show that MMP14 expression in stromal fibroblasts regulates melanoma tumor progression by modifying the peritumoral matrix and point to collagen accumulation as a negative regulator of melanoma.

The Hexosamine Biosynthetic Pathway as a Therapeutic Target after Cartilage Trauma: Modification of Chondrocyte Survival and Metabolism by Glucosamine Derivatives and PUGNAc in an Ex Vivo Model. Riegger J, Baumert J, Zaucke F, Brenner RE. Int J Mol Sci. 2021 Jul 6;22(14):7247. doi: 10.3390/ijms22147247.
Corresponding author: rolf.brenner@uni-ulm.de
Abstract: *The hexosamine biosynthetic pathway (HBP) is essential for the production of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), the building block of glycosaminoglycans, thus playing a crucial role in cartilage anabolism. Although O-GlcNAcylation represents a protective regulatory mechanism in cellular processes, it has been associated with degenerative diseases, including osteoarthritis (OA). The present study focuses on HBP-related processes as potential therapeutic targets after cartilage trauma. Human cartilage explants were traumatized and treated with GlcNAc or glucosamine sulfate (GS); PUGNAc, an inhibitor of O-GlcNAcase; or azaserine (AZA), an inhibitor of GFAT-1. After 7 days, cell viability and gene expression analysis of anabolic and catabolic markers, as well as HBP-related enzymes, were performed. Moreover, expression of catabolic enzymes and type II collagen (COL2) biosynthesis were determined. Proteoglycan content was assessed after 14 days. Cartilage trauma led to a dysbalanced expression of different HBP-related enzymes, comparable to the situation in highly degenerated tissue. While GlcNAc and PUGNAc resulted in significant cell protection after trauma, only PUGNAc increased COL2 biosynthesis. Moreover, PUGNAc and both glucosamine derivatives had anti-catabolic effects. In contrast, AZA increased catabolic processes. Overall, "fueling" the HBP by means of glucosamine derivatives or inhibition of deglycosylation turned out as cells and chondroprotectives after cartilage trauma.*

Collagen type VI is the antigen recognized by the ER-TR7 antibody. Schiavinato A, Przyklenk M, Kobbe B, Paulsson M, Wagener R. Eur J Immunol. 2021 Sep;51(9):2345-2347. doi: 10.1002/eji.202149263.
Corresponding author: aschiav1@uni-koeln.de
Abstract: *The monoclonal antibody ER-TR7 was used in a great number of studies for detecting reticular fibroblasts and the ECM of lymphoid and non-lymphoid organs even if the protein recognized by the ER-TR7 antibody was not known. We have now identified native collagen VI microfibrils as its tissue antigen.*

Autophagy: Instructions from the extracellular matrix. Schaefer L, Dikic I. Matrix Biol. 2021 Jun;100-101:1-8. doi: 10.1016/j.matbio.2021.06.002.
Corresponding author: schaefer@med.uni-frankfurt.de and Ivan.Dikic@biochem2.de
Abstract: *In recent years, extensive research has uncovered crucial regulatory roles for the extracellular matrix (ECM) in regulating autophagy. Autophagy is a ubiquitous and highly conserved catabolic process that allows the selective removal and recycling of cytosolic components via lysosomal or vacuolar degradation. Due to its pivotal role in cellular homeostasis, the impairment of autophagy is involved in the pathophysiology of numerous diseases, comprising infectious diseases, immune and neurodegenerative disorders, renal and hepatic diseases, intervertebral and cartilage disorders, as well as fibrosis and cancer. Several ECM-derived proteoglycans and proteins, including decorin, biglycan, endorepellin, endostatin, collagen VI, and plasminogen kringle 5, have been identified as strong inducers of autophagy. In contrast, laminin α2, perlecan, and lumican exert opposite function by suppressing autophagy. Importantly, by direct interaction with various receptors, which interplay with their co-receptors and adhesion molecules, the ECM is able to direct autophagy in a molecular and cell context-specific manner. Thus, vast pharmacological potential resides in translating this knowledge into the development of ECM-derived therapeutics selectively regulating autophagy.*

Biglycan: A regulator of hepatorenal inflammation and autophagy. Schulz M, Diehl V, Trebicka J, Wygrecka M, Schaefer L. Matrix Biol. 2021 Jun;100-101:150-161. doi: 10.1016/j.matbio.2021.06.001.
Corresponding author: schaefer@med.uni-frankfurt.de
Abstract: *Soluble biglycan, a small leucine-rich proteoglycan, plays a significant role in several pathologies as it has emerged as an extracellular matrix-derived danger-associated molecular pattern. Biglycan is released from the extracellular matrix in response to tissue injury and, as a canonical danger signal, interacts with innate immune receptors, Toll-like receptors 2 and 4, thereby triggering a sustained inflammatory response. Recent evidence indicates that biglycan acts as a molecular switch between inflammation and autophagy by a specific interaction with the Toll-like co-receptor CD14 and CD44, respectively. Biglycan-evoked autophagy further contributes to the anti-inflammatory M2 macrophage polarization, inflammation resolution and tissue repair. These multivalent roles of soluble biglycan have been well characterized in inflammatory kidney diseases. In chronic liver diseases, increased levels of soluble biglycan have been described for years, leading to utilization of biglycan serum levels as a non-invasive biomarker for fibrosis. Hepatorenal dysfunction represents a classic example of inter-organ crosstalk, in which functional and molecular alterations of the cirrhotic liver can promote the development of renal failure. In patients with liver cirrhosis, development of hepatorenal syndrome is associated with high mortality. In this review, we will discuss the crucial role of soluble biglycan in inflammation and autophagy and its possible implications for hepatorenal dysfunction. We propose a novel concept of hepatorenal crosstalk, that is, biglycan produced by the cirrhotic liver could constitute a circulating "messenger" for the kidneys triggering inflammation and/or autophagy ultimately affecting disease outcome.*

Syndecan-1 (CD138) as a Pathogenesis Factor and Therapeutic Target in Breast Cancer. Sheta M, Götte M. Curr Med Chem. 2021;28(25):5066-5083. doi: 10.2174/0929867328666210629122238.
Corresponding author: martingotte@uni-muenster.de
Abstract: *The successive stages of breast cancer growth and dissemination depend on cell-autonomous factors and the communication between tumor cells and their surrounding cellular and extracellular matrix microenvironment. The cell surface heparan sulfate proteoglycan Syndecan-1 is dysregulated both in tumor cells and cells of the breast tumor stroma, indicating a potential role in the pathogenesis of this most frequent malignancy in women. Indeed, Syndecan-1 interacts with numerous ligands and receptors relevant to tumor progression, affecting processes as diverse as cancer stem cell function, cell proliferation, apoptosis, cell adhesion, migration and invasion, tumor angiogenesis, and leukocyte function in the tumor stroma. The present review summarizes the current understanding of breast carcinogenesis in correlation with their Syndecan-1 expression, involved mechanisms, and proposed therapeutic strategies against Syndecan-1-related malignancy.*

Anti-Inflammatory Effects of Endogenously Released Adenosine in Synovial Cells of Osteoarthritis and Rheumatoid Arthritis Patients. Sohn R, Junker M, Meurer A, Zaucke F, Straub RH, Jenei-Lanzl Z. Int J Mol Sci. 2021 Aug 19;22(16):8956. doi: 10.3390/ijms22168956.
Corresponding author: zsuzsa.jenei-lanzl@kgu.de
Abstract: *Exogenous adenosine and its metabolite inosine exert anti-inflammatory effects in synoviocytes of osteoarthritis (OA) and rheumatoid arthritis (RA) patients. We analyzed whether these cells are able to synthesize adenosine/inosine and which adenosine receptors (ARs) contribute to anti-inflammatory effects. The functionality of synthesizing enzymes and ARs was tested using agonists/antagonists. Both OA and RA cells expressed CD39 (converts ATP to AMP), CD73 (converts AMP to adenosine), ADA (converts adenosine to inosine), ENT1/2 (adenosine transporters), all AR subtypes (A_1, A_{2A}, A_{2B} and A_3) and synthesized predominantly adenosine. The CD73 inhibitor AMPCP significantly increased IL-6 and decreased IL-10 in both cell types, while TNF only increased in RA cells. The ADA inhibitor DAA significantly reduced IL-6 and induced IL-10 in both OA and RA cells. The A_{2A}AR agonist*

CGS 21680 significantly inhibited IL-6 and induced TNF and IL-10 only in RA, while the A_{2B}AR agonist BAY 60-6583 had the same effect in both OA and RA. Taken together, OA and RA synoviocytes express the complete enzymatic machinery to synthesize adenosine/inosine; however, mainly adenosine is responsible for the anti- (IL-6 and IL-10) or pro-inflammatory (TNF) effects mediated by A_{2A}- and A_{2B}AR. Stimulating CD39/CD73 with simultaneous ADA blockage in addition to TNF inhibition might represent a promising therapeutic strategy.

Substance P and Alpha-Calcitonin Gene-Related Peptide Differentially Affect Human Osteoarthritic and Healthy Chondrocytes. Stöckl S, Eitner A, Bauer RJ, König M, Johnstone B, Grässel S. Front Immunol. 2021 Aug 27;12:722884. doi: 10.3389/fimmu.2021.722884.
Corresponding author: susanne.graessel@ukr.de
Abstract: *Osteoarthritis (OA) is a degenerative joint disease that not only causes cartilage loss but also structural damage in all joint tissues. Joints are innervated by alpha-calcitonin gene-related peptide (αCGRP) and substance P (SP)-positive sensory nerve fibers. Alteration of sensory joint innervation could be partly responsible for degenerative changes in joints that contribute to the development of OA. Therefore, our aim was to analyze and compare the molecular effects of SP and αCGRP on the metabolism of articular chondrocytes from OA patients and non-OA cartilage donors. We treated the cells with SP or αCGRP and analysed the influence of these neuropeptides on chondrocyte metabolism and modulation of signaling pathways. In chondrocytes from healthy cartilage, SP had minimal effects compared with its effects on OA chondrocytes, where it induced inflammatory mediators, inhibited chondrogenic markers and promoted apoptosis and senescence. Treatment with αCGRP also increased apoptosis and senescence and reduced chondrogenic marker expression in OA chondrocytes, but stimulated an anabolic and protective response in healthy chondrocytes. The catabolic influence of SP and αCGRP might be due to activation of ERK signaling that could be counteracted by an increased cAMP response. We suggest that a switch between the G-subunits of the corresponding receptors after binding their ligands SP or αCGRP plays a central role in mediating the observed effects of sensory neuropeptides on chondrocytes.*

Raman microspectroscopy and Raman imaging reveal biomarkers specific for thoracic aortic aneurysms. Sugiyama K, Marzi J, Alber J, Brauchle EM, Ando M, Yamashiro Y, Ramkhelawon B, Schenke-Layland K, Yanagisawa H. Cell Rep Med. 2021 Apr 28;2(5):100261. doi: 10.1016/j.xcrm.2021.100261.
Corresponding author: katja.schenke-layland@uni-tuebingen.de
Abstract: *Aortic rupture and dissection are life-threatening complications of ascending thoracic aortic aneurysms (aTAAs), and risk assessment has been largely based on the monitoring of lumen size enlargement. Temporal changes in the extracellular matrix (ECM), which has a critical impact on aortic remodeling, are not routinely evaluated, and cardiovascular biomarkers do not exist to predict aTAA formation. Here, Raman microspectroscopy and Raman imaging are used to identify spectral biomarkers specific for aTAAs in mice and humans by multivariate data analysis (MVA). Multivariate curve resolution-alternating least-squares (MCR-ALS) combined with Lasso regression reveals elastic fiber-derived (Ce1) and collagen fiber-derived (Cc6) components that are significantly increased in aTAA lesions of murine and human aortic tissues. In particular, Cc6 detects changes in amino acid residues, including phenylalanine, tyrosine, tryptophan, cysteine, aspartate, and glutamate. Ce1 and Cc6 may serve as diagnostic Raman biomarkers that detect alterations of amino acids derived from aneurysm lesions.*

New Insights into Xenotransplantation for Cartilage Repair: Porcine Multi-Genetically Modified Chondrocytes as a Promising Cell Source. Tritschler H, Fischer K, Seissler J, Fiedler J, Halbgebauer R, Huber-Lang M, Schnieke A, Brenner RE. Cells. 2021 Aug 20;10(8):2152. doi: 10.3390/cells10082152.
Corresponding author: rolf.brenner@uni-ulm.de
Abstract: *Transplantation of xenogenic porcine chondrocytes could represent a future strategy for the treatment of human articular cartilage defects. Major obstacles are humoral and cellular rejection processes triggered by*

xenogenic epitopes like α-1,3-Gal and Neu5Gc. Besides knockout (KO) of genes responsible for the biosynthesis of respective epitopes (GGTA1 and CMAH), transgenic expression of human complement inhibitors and anti-apoptotic as well as anti-inflammatory factors (CD46, CD55, CD59, TNFAIP3 and HMOX1) could synergistically prevent hyperacute xenograft rejection. Therefore, chondrocytes from different strains of single- or multi-genetically modified pigs were characterized concerning their protection from xenogeneic complement activation. Articular chondrocytes were isolated from the knee joints of WT, GalTKO, GalT/CMAH-KO, human CD59/CD55//CD46/TNFAIP3/HMOX1-transgenic (TG), GalTKO/TG and GalT/CMAHKO/TG pigs. The tissue-specific effectiveness of the genetic modifications was tested on gene, protein and epitope expression level or by functional assays. After exposure to 20% and 40% normal human serum (NHS), deposition of C3b/iC3b/C3c and formation of the terminal complement complex (TCC, C5b-9) was quantified by specific cell ELISAs, and generation of the anaphylatoxin C5a by ELISA. Chondrocyte lysis was analyzed by Trypan Blue Exclusion Assay. In all respective KO variants, the absence of α -1,3-Gal and Neu5Gc epitope was verified by FACS analysis. In chondrocytes derived from TG animals, expression of CD55 and CD59 could be confirmed on gene and protein level, TNFAIP3 on gene expression level as well as by functional assays and CD46 only on gene expression level whereas transgenic HMOX1 expression was not evident. Complement activation in the presence of NHS indicated mainly effective although incomplete protection against C3b/iC3b/C3c deposition, C5a-generation and C5b-9 formation being lowest in single GalTKO. Chondrocyte viability under exposure to NHS was significantly improved even by single GalTKO and completely preserved by all other variants including TG chondrocytes without KO of xenoepitopes.

Syndecan-1 Depletion Has a Differential Impact on Hyaluronic Acid Metabolism and Tumor Cell Behavior in Luminal and Triple-Negative Breast Cancer Cells. Valla S, Hassan N, Vitale DL, Madanes D, Spinelli FM, Teixeira FCOB, Greve B, Espinoza-Sánchez NA, Cristina C, Alaniz L, Götte M. Int J Mol Sci. 2021 May 30;22(11):5874. doi: 10.3390/ijms22115874.

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Abstract: *Glycosaminoglycans (GAGs) and proteoglycans (PGs) are major components of the glycocalyx. The secreted GAG and CD44 ligand hyaluronic acid (HA), and the cell surface PG syndecan-1 (Sdc-1) modulate the expression and activity of cytokines, chemokines, growth factors, and adhesion molecules, acting as critical regulators of tumor cell behavior. Here, we studied the effect of Sdc-1 siRNA depletion and HA treatment on hallmark processes of cancer in breast cancer cell lines of different levels of aggressiveness. We analyzed HA synthesis, and parameters relevant to tumor progression, including the stem cell phenotype, Wnt signaling constituents, cell cycle progression and apoptosis, and angiogenic markers in luminal MCF-7 and triple-negative MDA-MB-231 cells. Sdc-1 knockdown enhanced HAS-2 synthesis and HA binding in MCF-7, but not in MDA-MB-231 cells. Sdc-1-depleted MDA-MB-231 cells showed a reduced CD24-/CD44+ population. Furthermore, Sdc-1 depletion was associated with survival signals in both cell lines, affecting cell cycle progression and apoptosis evasion. These changes were linked to the altered expression of KLF4, MSI2, and miR-10b and differential changes in Erk, Akt, and PTEN signaling. We conclude that Sdc-1 knockdown differentially affects HA metabolism in luminal and triple-negative breast cancer model cell lines and impacts the stem phenotype, cell survival, and angiogenic factors.*

Controlling BMP growth factor bioavailability: The extracellular matrix as multi skilled platform. Zimmermann LA, Correns A, Furlan AG, Spanou CES, Sengle G. Cell Signal. 2021 Sep;85:110071. doi: 10.1016/j.cellsig.2021.110071.

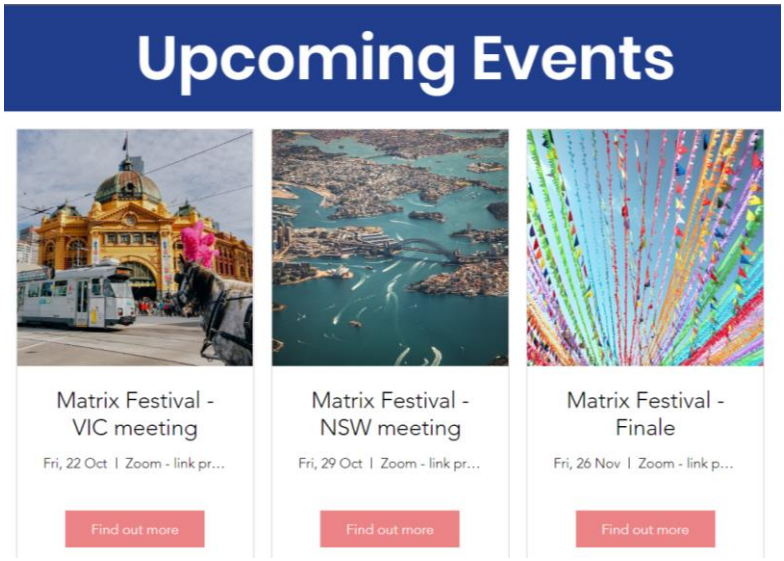
Corresponding author: gsengle@uni-koeln.de

Abstract: *Bone morphogenetic proteins (BMPs) belong to the TGF-β superfamily of signaling ligands which comprise a family of pluripotent cytokines regulating a multitude of cellular events. Although BMPs were originally discovered as potent factors extractable from bone matrix that are capable to induce ectopic bone formation in*

soft tissues, their mode of action has been mostly studied as soluble ligands in absence of the physiologically relevant cellular microenvironment. This micro milieu is defined by supramolecular networks of extracellular matrix (ECM) proteins that specifically target BMP ligands, present them to their cellular receptors, and allow their controlled release. Here we focus on functional interactions and mechanisms that were described to control BMP bioavailability in a spatio-temporal manner within the respective tissue context. Structural disturbance of the ECM architecture due to mutations in ECM proteins leads to dysregulated BMP signaling as underlying cause for connective tissue disease pathways. We will provide an overview about current mechanistic concepts of how aberrant BMP signaling drives connective tissue destruction in inherited and chronic diseases

Meeting announcements

MBSANZ
MATRIX BIOLOGY SOCIETY OF AUSTRALIA AND NEW ZEALAND



Matrix Biology Festival organised in Australia. It is a hybrid format and will be streamed online so our international matrix colleagues may wish to join. between September and November 2021 (https://www.mbsanz.org/events).

The 5th National Conference of Chinese Society of Matrix Biology (CSMB)

SHANGHAI CANCER INSTITUTE

SUZHOU MUNICIPAL HOSPITAL

October 21th-23th, 2021

Suzhou, Jiangsu Province, China

Sponsor

Chinese Society of Matrix Biology (CSMB)

Organizer

Shanghai Cancer Institute, Suzhou Municipal Hospital

Topics

Matrix biology,
Stem cell biology and applications,
Tissue microenvironment and cancer metastasis

President

Zhi-Gang Zhang (Shanghai), Kang-Yun Sun (Suzhou)

Co-Presidents

Hong-Quan Zhang (Beijing), Jian-Feng Chen (Shanghai), Wei Kong (Beijing),
Zhen-Sheng Chen (Hongkong), Lu-Yang Yu (Hangzhou),
Gao-Xiang Ge (Shanghai), Gao-Liang Ouyang (Xiamen)

Date: October 21th-23th, 2021 (Registration on October 21th, 2021; Conference Program during October 22th-23th, 2021)

Venue: Suzhou, Jiangsu Province, China, Email: csmb2016@163.com

Abstract Submission

The conference includes Invited Talks, Oral Presentations and Poster Presentations. The Oral and Poster Presentation are currently open for abstract submission. To encourage the participation of young scholars, the organization committee will provide Travel Award for 6 young scholars selected by academic committee based on the submitted abstracts.

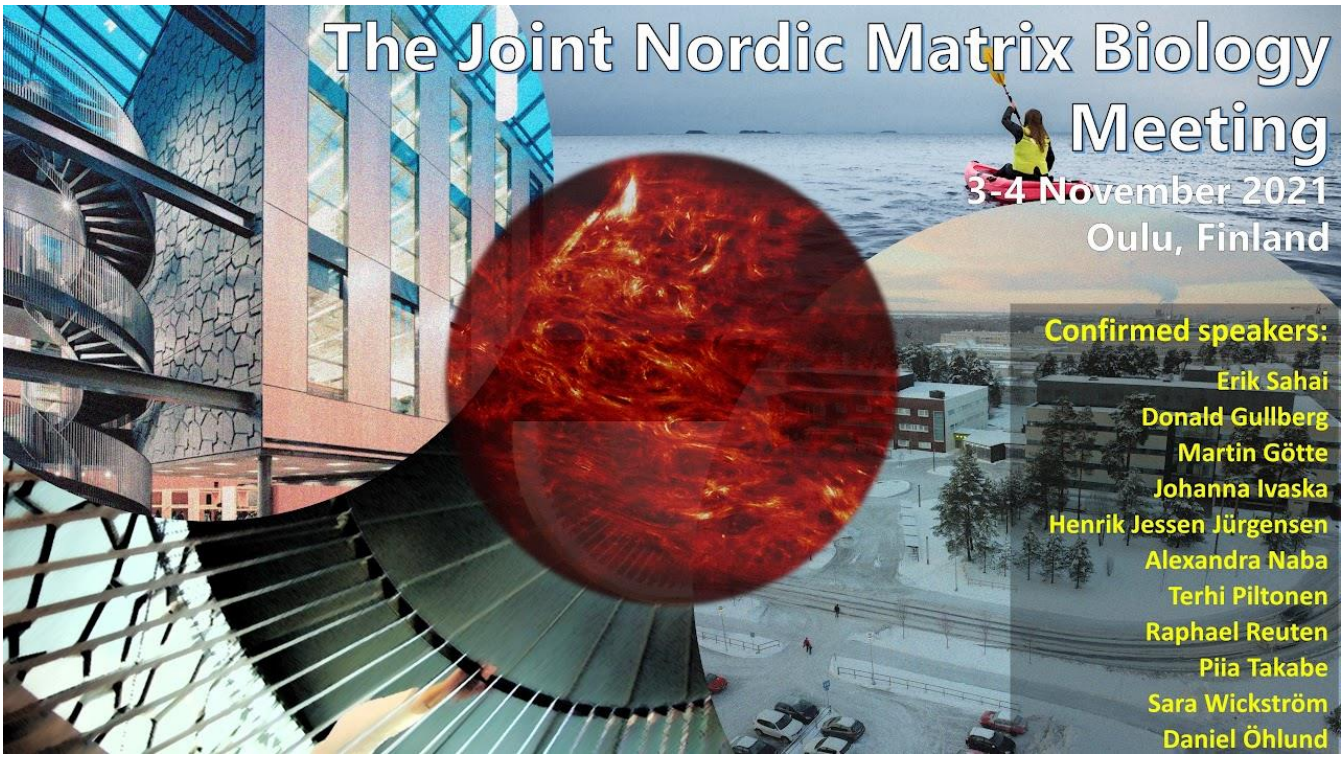
Abstract must be in English with less than 500 words and displayed in single-spaced with 11 point Font of Times New Roman. Please submit abstract before August 31, 2021 and define it for application of oral or poster presentations. For more detailed information of abstract submission, please contact us through email: **csmb2016@163.com.**

Requirements for the applicants of Travel Award:

1) The applicant should be either post-doc or graduate student under 40-year old (born after Jan 1st, 1976).
2) The applied work should be related to matrix biology area as basic, translational or methodology studies.
3) The applied work should be unpublished.
4) The applicant should address the application of "Travel Grant" in the abstract

The Joint Nordic Matrix Biology Meeting
Oulu (Finland) 3-4 November 2021

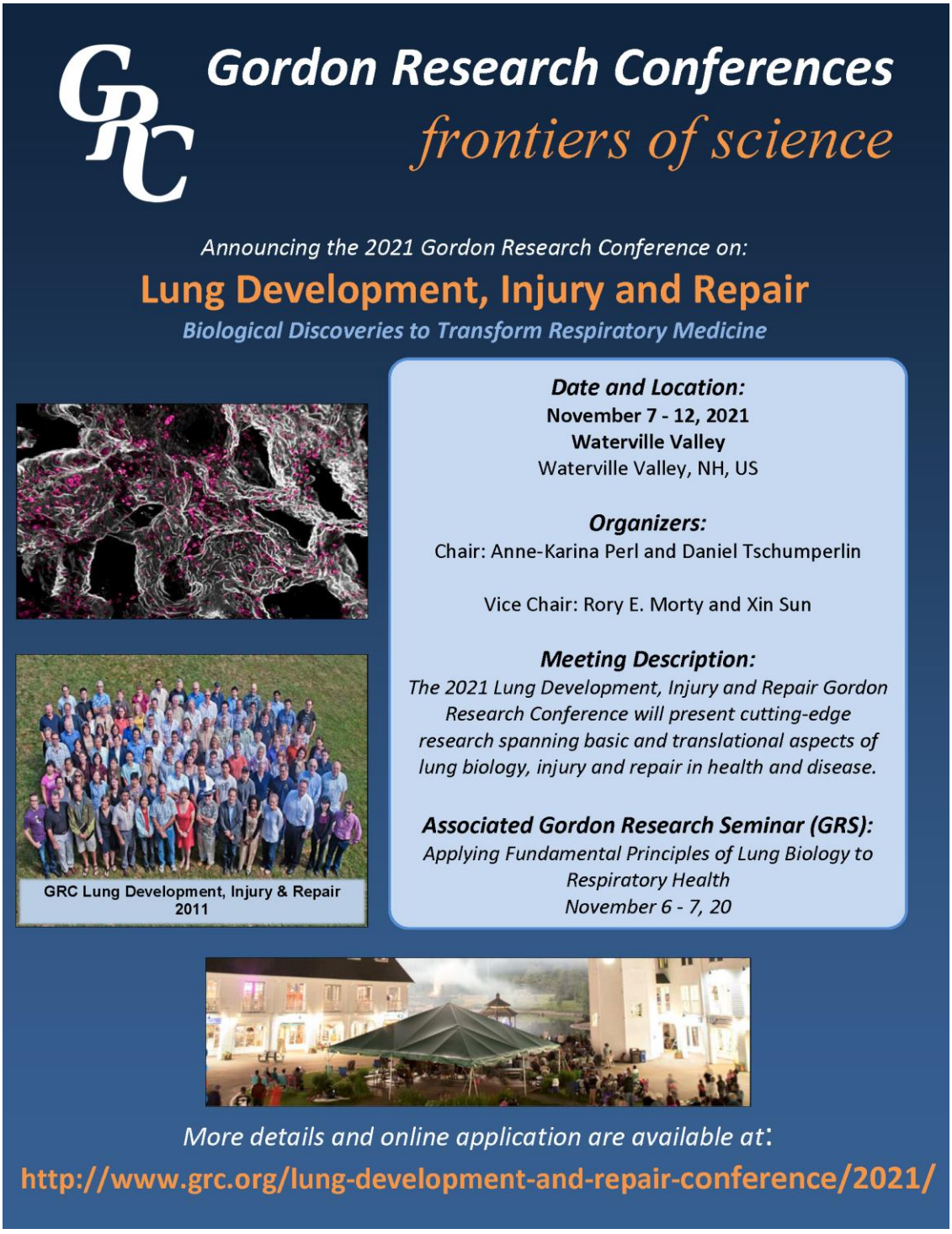
https://www.sidekudostutkijat.fi/the-joint-nordic-matrix-biology-meeting



Lung Development, Injury and Repair GRC (November 7-12, 2021)

Waterville Valley, NH, USA

https://www.grc.org/lung-development-injury-and-repair-conference/2021/



FEBS Advanced Lecture Course
Matrix Pathobiology, Signaling and Molecular Targets
The Island of Crete - Greece, 5-10 May 2022

https://mpst2022.febsevents.org

Deadlines

- **Applications Opening** now open
- **Youth Travel Fund Grants** Deadline January 21, 2022
- **Applications Closing** February 4, 2022

Dear Colleagues and Friends,

On behalf of the Organizing Committee, it is a pleasure to invite you to the 8th FEBS Advanced Lecture Course on Matrix Pathobiology, Signaling and Molecular Targets, to be held in Aldemar Knossos Royal's conference center (https://www.aldemarknossosroyal.gr/events/conferences/) on 5th to 10th May 2022.

Cell biology and biochemistry have recently increasingly turned their attention to the space between cells and revealed an elaborate network of macromolecules essential for structural support, cell migration, adhesion and signaling. The 6-days meeting will offer oral sessions with invited plenary lectures, talks by confirmed speakers, general lectures and tutorials, selected talks related to the topics of the presented abstracts, poster and flash presentations, panel discussions and speakers' corner/meet the experts. These sessions will address both basic and applied science topics that appeal to the range of participants working in the fields of matrix organization and assembly, cell adhesion, matrix-mediated signaling, as well as the matrix macromolecular effectors, namely proteoglycans and glycans, integrins, novel collagen types, growth factors and matrix metalloproteinases and other matrix degrading enzymes that affect the cell behavior.

The Organizing Committee has put together an outstanding group of internationally recognized experts as invited speakers. Open slots for talks will include selected short talks, flash poster presentations, and confirmed registered speakers as well. The lectures and tutorials will provide you with an update of important new knowledge covering key areas of the field. Young Travel Fellowships and Young Investigator Awards will also be available upon application/selection procedure for graduates and fellows up to 5-years after their PhD.

The most important goal of this meeting is to bring together scientists from biochemistry, life sciences, molecular cell biology and bioinformatics on an important and fast growing scientific field and to create the environment for a superb science, warm collegiality, an all-around rewarding experience and social events during this special time of the year.

We are looking forward to welcome you in Greece for an exciting and memorable scientific meeting.

Nikos Karamanos, Chairman of the Organizing Committee

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

Proctor Academy, Andover, NH, USA

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

Save the date!
MBE2022 - September 28-30, 2022
Florence (Italy)

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

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

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)

Gordon Research Conferences
Frontiers of Science

https://www.grc.org/elastin-elastic-fibers-and-microfibrils-conference/2021/

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)

Like ISMB on Facebook
https://www.facebook.com/IntSocMatBio/

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

Communication group coordinated by Julia Etich (Germany, Julia.Etich@kgu.de)
Valerio Izzi (Finland, Valerio.Izzi@oulu.fi)
Pauline Nauroy, University of Freiburg (Germany) pauline.nauroy@uniklinik-freiburg.de, @PaulineNauroy)
Chloé Yeung (Institute of Sports Medicine Copenhagen Denmark, chloe.yeung@gmail.com, @ccstorytime)
The ISMB correspondents of National Societies for Matrix Biology for Facebook & Twitter

ISMB correspondents of National Societies for Matrix Biology for Facebook & 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, Goethe University Frankfurt (Germany) julia.etich@kgu.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 Rousselle, University of Lyon (France) Patricia.rousselle@ibcp.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
Alexandre Trotier, National University of Ireland, Galway (Ireland) A.TROTIER1@nuigalway.ie

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
Collin Ewald, ETH Zurich (Switzerland) collin-ewald@ethz.ch