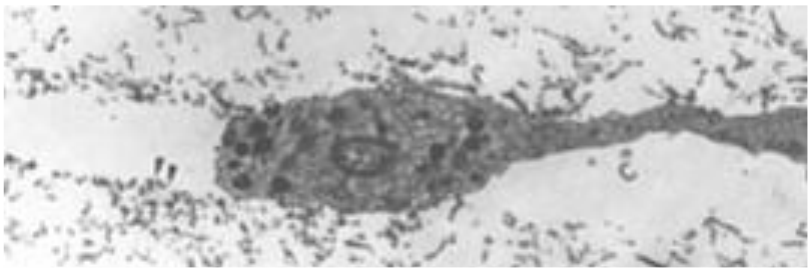


A fibroblast within a tethered lattice, after 13 days, with a cavity surrounding the cell and areas of packed collagen fibrils *(Porter et al. 1998 Wound Rep. Reg. 6: 157-166)*

ISMB NEWSLETTER 44 May 2023 Editor: Sylvie Ricard-Blum

FROM THE PRESIDENT'S DESK

Dear ISMB members, friends, and colleagues,

The major goals of the ISMB are to promote extracellular matrix research worldwide, and to facilitate the professional development of early career researchers. Leaving now the pandemic behind after three years, we are heading back to normal and are delighted to advertise excellent and eminent conferences taking place again on-site. Among those, the ISMB is supporting the Gordon Research Conference & Gordon Research Seminar on Collagens (July 9-14, 2023, Colby-Sawyer College, NH, USA). To help junior scientists participate in international meetings relevant to matrix biology, ISMB offers international travel grants. The ISMB considers these to be one of the society's priorities and is looking forward to revive them. The travel grant application is now made directly available to our membership via the web page (https://www.ismb.org/copy-of-travel-grants). Please consider that the next international travel grant application deadline is July 1st, 2023.

The only source of ISMB's income is from our membership fees. Big thanks to all of you who have already paid this year! All others we would like to encourage to renew their membership for 2023 via our web page (https://www.ismb.org/join). Please pass this newsletter also on to your students, post-docs and other matrix biology colleagues and encourage them to join ISMB.

We are very pleased to let you know that CY Chloé Yeung (Denmark) and Thomas R. Cox (Australia) have been elected unopposed to regular Council members and now the ISMB Council is complete. We warmly thank Wei Kong (China) and Gerhard Sengle (Germany) who served for 6 years each at the ISMB Council and were willing to invest a significant fraction of their time into a service for the Society. Chloé and Tom will surely bring fresh ideas and innovation into the ISMB Council and the society's activities. We congratulate Chloé and Tom on starting their service on the Council.

Moreover, the ISMB communication team is seeking motivated junior matrix researchers volunteering to help increasing the visibility and popularity of the ISMB on social media and through our web page. Interested junior members are welcome to contact the coordinator of the team (Valerio Izzi, valerio.izzi@oulu.fi).

Lastly, the ISMB Distinguished Investigator Awardee Taina Pihlajaniemi will deliver her lecture on «Transmembrane and Multiplexin Collagens in Development and Pathobiology» at the biennial meeting of the ASMB that will be held as a joint meeting with the American Society for Investigative Pathology and The Histochemical Society on October 22-25, 2023 in beautiful Salt Lake City, Utah, USA. Once again, our warmest congratulations to Taina for receiving the award recognizing her outstanding contribution to collagen research.

Enjoy this exceptional issue of the ISMB newsletter and thank our newsletter editor Sylvie Ricard-Blum for keeping the success of the newsletters at a constantly high level.

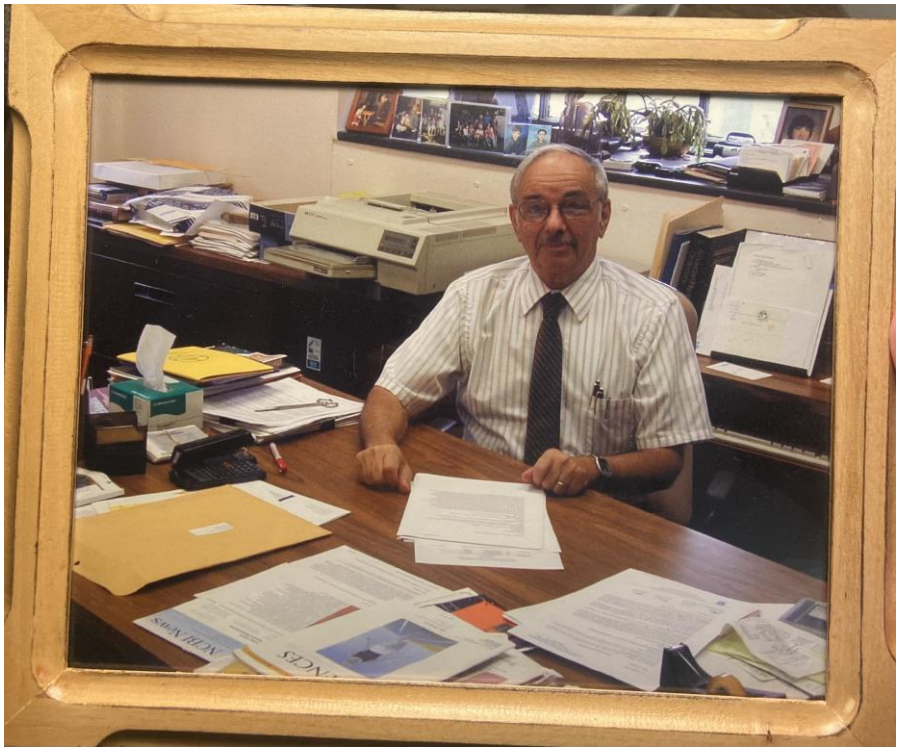
Nikos Karamanos, ISMB President (n.k.karamanos@upatras.gr), and Julia Etich, ISMB Secretary (julia.etich@uni-koeln.de)

Content

Obituary

ARTHUR VEIS

Arthur Veis, PhD, passed away Sunday April 23 at age 97.



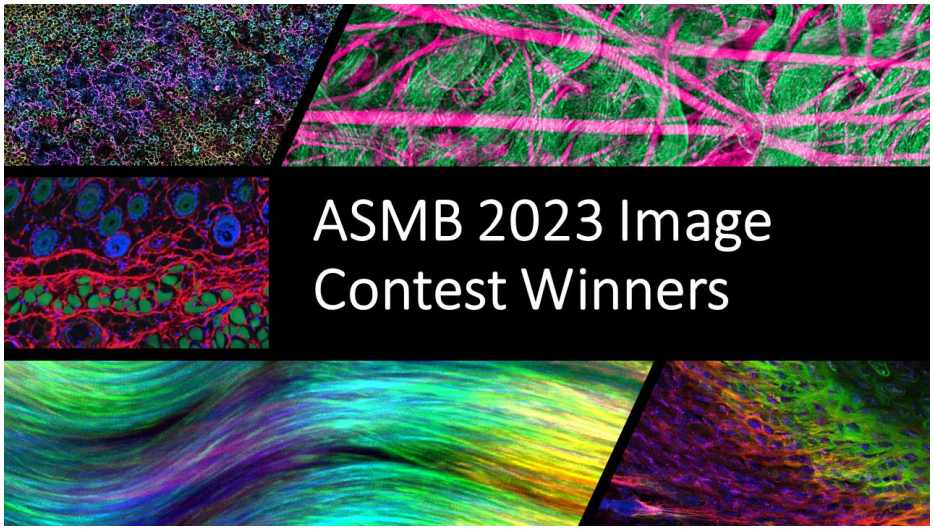
He lived a full life. Born in Pittsburgh in 1925, he moved with his family in the depression to Chicago and stayed a die-hard Chicagoan for the rest of his life. After graduating high school in 1943, he spent a year in college prior to joining the Navy (in spite of not knowing how to swim). After officer training, he ended up on the USS Baltimore, an aircraft carrier, helping planes take off and land. He arrived in Japan just as the war ended and ran the Navy taxi service between vessels and shore, and gave tours of some of the bomb sites. Once home, he completed college and moved back to Chicago for his PhD studies at Northwestern University.

On his first publication, of his doctoral work, "The interactions of the alkali ions with some linear polyelectrolytes," he was the sole author. After spending 8 years studying collagen at Armour Company, he joined the faculty at Northwestern in 1960, where he remained until publishing his last paper in Connective Tissue Research in 2018 at age 92! In those 66 years as a working scientist, Art published over 250 articles on a wide range of topics in connective tissue biology, including the structure of collagen and its associated proteins, interactions with water, biomineralization, and complex coacervation. He was Editor-in-Chief of Connective Tissue Research for more than 25 years, from 1984-2012. He and his wife Eve traveled the world, often planning trips around scientific meetings. He met both Linus Pauling and Francis Crick at a conference in England in 1957. Sabbaticals were spent at Stanford, the European Molecular Biology Laboratory in Grenoble, France, and at the Weizmann Institute in Israel. Art founded the International Conference on the Chemistry and Biology of Mineralized Tissues (first meeting in 1981, now heading into its 14th meeting). Throughout his career, Art supported and mentored many researchers, becoming lifelong friends with many. To him, they were truly his scientific family. Art was also extremely proud of his three children and seven grandchildren, whom he valued as individuals and who all respected and adored him. He will be greatly missed.

News from national societies

The American Society for Matrix Biology (ASMB)

The ASMB Image Contest winners have been announced. One of the selected winners, Neha Dinesh, is from ISMB. The link to the image contest webpage where you can learn more about the selected images is https://asmb.memberclicks.net/image-contest-winners-2023.



Looking for a position

Collin Y. Ewald, Ph.D. is looking for a new academic position.

Current position: tenure track Assistant Professor (SNF professorship)
Institute of Translational Medicine/ Department of Health Sciences and Technology, ETH Zürich/ Switzerland.
E-mail: collin-ewald@ethz.ch,

- Led research team of 4 Ph.D. students and 2 postdocs, 1 Guest Professor, 17 Master Students / 2 Medical Students / 4 Bachelor Students / 3 High School Students.
- 37 peer-reviewed publications from my independent lab (last 7 years), and 31 (co-)corresponding PI (and/or last author)
- 1 patent filed
- Total 3rd Party funds raised (2016-2022): 3.5 million CHF
- Certified Good Clinical Practice GCP1-3, Animal experimentation license LTK1-2 (mice, rats), induced pluripotent stem cells (iPSC; DRC Harvard Medical School)
- 10 Chair and 10 doctoral examinations (Ph.D. defenses)
- 4 keynote talks, 30 invited talks at international conferences (including WEF)
- 3 international and 4 national conferences co-organized

- 20 Interviews in newspapers, news media, and podcast
- 44 peer-reviewed publications, including Nature (IF=69), Nature communications (IF=18), Small (IF=15), Aging Cell (IF=11), eLife (IF=9) as first or corresponding author, cited more than 1457 times, with an h-index of 19 (Google Scholar, April 2023).

My laboratory (http://ewaldlab.com) studies mechanisms that promote extracellular matrix (ECM) homeostasis and longevity. We unravel the basic principles using C. elegans as a multicellular/tissue in-vivo and non-invasive model for ECM turnover and dynamics during aging. We then use human cell culture and mouse models to translate the initial findings. Our research uncovered a novel mechanotransductive mechanism (hemidesmosome-YAP1 signaling) for the importance of healthy lifespan extension. Strikingly, mutations in hemidesmosomes lead to severe skin fragility and a clinical need for novel treatments. Our current efforts center around providing new mechanistic targets for novel treatments for these patients, which, if clinical trials are successful, could be applied to the elderly, promoting health during old age.

We employ molecular and systems biological approaches using omics data of humans to elucidate targets and mechanisms in model organisms combined with in-vivo high throughput screens to identify drug candidates and artificial intelligence to drive therapeutic discovery and translational medicine. Developed techniques and methods (CRISPR activation, AID-RNAi, and acoustophoretic microfluidics) to address unmet needs.

PhD, post-doctoral and other positions

Vacancy for a permanent Lecturer position in Regenerative Medicine/Stem Cell Biology, Division of Cell Matrix Biology & Regenerative Medicine, University of Manchester (UK)

We invite applications for a Lecturer in Regenerative Medicine or Stem Cell Biology. Working collaboratively, you will be a future leader/ leader in your field, with a strong track record of research and publication in an area of Regenerative Medicine or Stem Cell Biology.

https://www.jobs.manchester.ac.uk/displayjob.aspx?jobid=25286&isPreview=Yes&advert=external
Closing date is 11th May 2023

The University of Münster (Germany) has announced a new call for the WiRe 'Women in Research' fellowships.

These fellowships are directed at female postdoctoral scientists (or beyond) who are at a decisive point of her career and who have the potential and vision to make a career in science. The fellowships are for 4-8 months (https://www.uni-muenster.de/forschung/en/wissenschaftler/wire/index.html)

If you are interested in applying please contact Prof. Dr. Martin Götte, Universitätsklinikum Münster, Germany (Martin.Goette@ukmuenster.de) to develop a proposal with his laboratory.

POST-DOCTORAL POSITION IN ONCO-IMMUNOLOGY

OREND -Tumor Microenvironment Laboratory
HOPITAL CIVIL
Institut d'Hématologie et d'Immunologie
INSERM U1109, France

The OREND laboratory reveals molecular mechanisms of how the extracellular matrix in cancer can be targeted for improving cancer therapy. An important strategy in cancer therapy is targeting of immune checkpoints. However, this strategy is limited by the cancer specific extracellular matrix where highly abundant tenascin-C is orchestrating an immune suppressive tumor microenvironment. Based on our discoveries about tenascin-C actions in immune suppression contributing to the immune exclusion phenotype we developped specific strategies to restore anti-tumor immunity which is monitored in specific tumor models that phenocopy human cancer (Fonta 2023, ***Matrix Biol;*** Loustau 2022, ***Matrix Biol;*** Yilmaz 2022, ***J Cell Sci;*** Murdamoothoo 2021, ***EMBO Mol Med;*** Dhaouadi et al 2021, ***Front Immunol;*** Deligne 2020, ***Cancer Immun Res;*** Spenle 2020, ***Cancer Immun Res).*** To strengthen our research in this exciting translational project we are looking for highly ambitioned postdoctoral candidates. The appointed postdoc will use state of the art technology in immunology and matrix research and will work within a consortium of colleagues experienced in matrix biology, immunology, omics and network analysis in frame of the INCa funded **TENMAX** project. Aims of this project are to (1) understand and (2) target the tumor immuno-landscape for developing novel anti-cancer targeting strategies.

The position is located at the Institut d'Hématologie et d'Immunologie in the center of Strasbourg (France) and is available for 24 months, starting in June 2023. **INSERM U1109** (https://www.canceropole-est.org/la-recherche/annuaire-du-canceropole-est/entreprises/detail?id=45) is associated with the University of Strasbourg and with the Doctoral School of Life Sciences and Health. It hosts 9 research teams with over 100 staff members. The institute is known for its expertise in immunogenetics and research in immune diseases, virology and cancer. It is equipped with staffed high-end technological platforms in immunology research, gene expression analysis and imaging.

Profile: We are looking for a highly motivated candidate with a recent PhD in tumor immunology or related fields and an excellent academic record. The candidate must have a strong background in tumor molecular biology and experience in murine tumor models, histology, cell culture, biochemistry and flow cytometry. Specific expertise in bioinformatics is a plus. The candidate should be able to think independently and creatively, and have excellent written and oral communication skills in English. The candidate shall work well in the team, supervise Master and PhD students, and present the project and results to scientists and the public. She/he will participate in extensive collaborations with the 5 partner laboratories involved in the project.

Application: Please send a motivation letter expressing your interest and suitability for the project, CV and publication list, and the names and e-mail addresses of two references. For further details and information see https://orend-tme-group.com, and contact Gertraud Orend: gertraud.orend@inserm.fr. The position will remain open until filled.

Spotlights on methods that other ISMB members may find useful

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

In Focus

Proteoglycan expression studied by microRNAs.
Espinoza-Sanchez NA, Troschel F, Greve B, Götte M. Methods Mol Biol. 2023;2619:273-292. doi: 10.1007/978-1-0716-2946-8_20.
Corresponding author: mgotte@uni-muenster.de
Abstract: MicroRNAs are small noncoding RNAs that regulate gene expression at the posttranscriptional level. Proteoglycans are glycoproteins characterized by covalent attachment of a glycosaminoglycan chain, which have been identified as regulatory targets of microRNAs in a physiological and pathophysiological context. We present a strategy and detailed methods for the functional analysis of microRNA regulation of proteoglycans using human cancer cells as an application example. The experimental setup includes in silico microRNA target prediction, transfection of cancer cells with microRNA precursors, validation of target regulation by qPCR, flow cytometry and luciferase reporter assays, and an example for functional analysis and phenotype confirmation by complementation analysis.

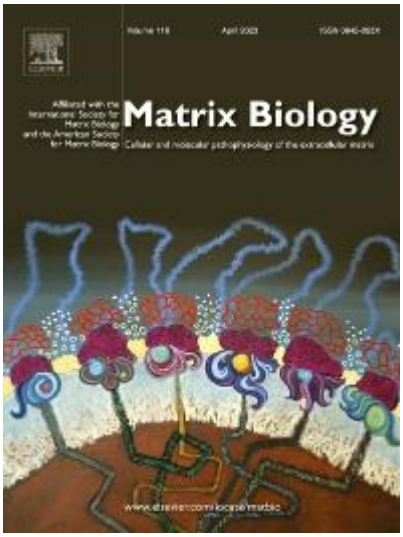
Evaluation of the *in vitro* and *in vivo* effects of biglycan in innate immunity.
Zeng-Brouwers J, Huber LS, Merline R, Trebicka J, Wygrecka M, Schaefer L. Methods Mol Biol. 2023;2619:109-124. doi: 10.1007/978-1-0716-2946-8_9.
Corresponding author: schaefer@med.uni-frankfurt.de
Abstract: Biglycan, a small leucine-rich proteoglycan (SLRP), is a crucial component of the extracellular matrix (ECM) associated with the maintenance of tissue homeostasis. In response to tissue damage, the ECM-derived soluble form of biglycan acts as a danger signal by triggering an inflammatory response via the toll-like receptor (TLR)2/TLR4 in macrophages and dendritic cells. The impact and signaling mechanism of biglycan in innate immunity is better understood with the use of specific and reliable research tools and investigation techniques. Accordingly, our lab has established explicit and detailed experimental protocols to examine the in vitro and in vivo effects of biglycan in cellular immune responses. To evaluate the in vitro effects of biglycan on macrophage activation, a comprehensive protocol that makes use of murine peritoneal macrophages has been described. Further, to study the in vivo effects of biglycan, a method that uses a pLIVE vector to generate transgenic mice transiently overexpressing human biglycan is detailed. A step-by-step protocol for analyzing the effects of soluble biglycan overexpression in transgenic mice is explained under the following sections: (1) construction of pLIVE-hBGN plasmid, (2) intravenous delivery of transgenic vector, (3) identification of hBGN transgene in hepatocytes (4) detection of transgenic biglycan protein in the plasma of transgenic mice, and (5) evaluation of the presence and pro-inflammatory effects of transgenic biglycan in extrahepatic mouse tissues.

Building, Visualizing, and Analyzing Glycosaminoglycan-Protein Interaction Networks
Ricard-Blum S. Methods Mol Biol . 2023;2619:211-224. doi: 10.1007/978-1-0716-2946-8_15.
Corresponding author: sylvie.ricard-blum@univ-lyon1.fr
Abstract: This chapter describes how to generate, visualize, and analyze interaction networks of glycosaminoglycans (GAGs), which are linear polyanionic polysaccharides mostly located at the cell surface and in the extracellular matrix. The protocol is divided into three major steps: (1) the collection of GAG-mediated interaction data, (2) the visualization of GAG interaction networks, and (3) the computational enrichment

analyses of these networks to identify their overrepresented features (e.g., protein domains, location, molecular functions, and biological pathways) compared to a reference proteome. These analyses are critical to interpret GAG interactomic datasets, decipher their specificities and functions, and ultimately identify GAG-protein interactions to target for therapeutic purpose.

Extracellular Matrix special Issues & journals

Matrix in Medicine Series Announcement



The extracellular matrix constitutes a major portion of the human body. It plays a key role in the structural organization of tissues, providing them with strength, rigidity, or elasticity, serving as a barrier, and ensuring tissue/organ compartmentalization. The extracellular matrix interacts with most cell types, and cell-matrix interactions regulate essential cellular functions including differentiation, proliferation, migration, and cell survival/cell death. Interactions of extracellular matrix with growth factors and other regulatory molecules are also critical in tissue homeostasis. The extracellular matrix is required for normal development and physiology, but it also is responsive to both acute and chronic injury and plays a crucial role in tissue repair and regeneration. Given the importance of extracellular matrix in human physiology, alterations in its composition, functions, and interactions with cells and secreted molecules are implicated in a vast array of human genetic and acquired diseases. Thus, a better understanding of the roles of the extracellular matrix and of cell-matrix interactions in human disease has the potential to identify novel factors in disease pathogenesis and to lead to design of new, targeted therapeutic approaches to treat human diseases.

To highlight the importance of extracellular matrix and cell-matrix interactions in the pathogenesis of human disease, we are introducing a special section in *Matrix Biology* called “Matrix in Medicine.” Review articles published in the “Matrix in Medicine” series are intended for both scientists and clinicians and should emphasize the relevance of extracellular matrix to fundamental biological processes involved in human diseases. These articles will discuss the clinical aspects of a particular human disease with an emphasis on the underlying extracellular matrix-focused molecular mechanisms in the disease pathogenesis and/or potential for extracellular matrix targeted therapeutic interventions. The intent is to publish at least one “Matrix in Medicine” review in each of the 8 yearly issues of Matrix Biology.

Submissions should highlight the role of extracellular matrix in important clinical problems and will undergo rigorous peer review characteristic of all submissions to Matrix Biology. Articles should be submitted through the “Matrix in Medicine” submission option at the Matrix Biology website https://www.sciencedirect.com/journal/matrix-biology.

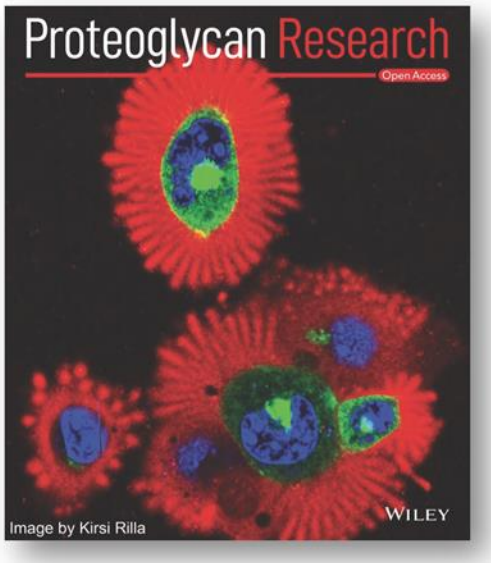
May 2023

Dear Proteoglycan Researchers,

I hope this finds you well. The journal is proceeding strongly. We have already published two papers: my editorial and a nice research report from Ralph Sanderson entitled "*Extracellular vesicles released during hypoxia transport heparanase and enhance macrophage migration, endothelial tube formation and cancer cell stemness*". This paper is accessible to everyone via PubMed since *Proteoglycan Research* is an open access journal (PMID: 37091070).

Additionally, we have two nice minireviews in press, one by Mary Cowman and Eva Turley on hyaluronan, CD44 and RHAMM, and one from Jorge Filmus focused on the biology of Glypicans, 35 years later. Three additional research papers are under review with more coming throughout the month.

As I mentioned before, *Proteoglycan Research* considers both mechanistic and correlative papers including research articles, research reports, full- length and mini-reviews, perspectives, methods papers and technical advances. Please view the Guide to Authors for more information.

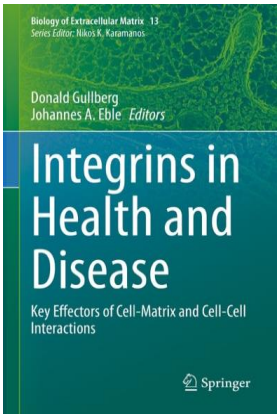


It would be a great opportunity if you could submit research papers from your lab and co-workers. If you are interested in writing a minireview or a perspective focused on emerging fields of research in proteoglycans, please contact me directly with your idea/proposal via e-mail to renato.iozzo@jefferson.edu. Also, ideas about special issues and guest editors are currently welcome.

I wish you a great spring and I will see many of you soon at the ISHAS meeting in Portland or at the Harden Conference on Proteoglycans in the UK.

All the best,

Renato V. Iozzo, MD PhD
Editor-In-Chief, Proteoglycan Research



Integrins in Health and Disease. Key Effectors of Cell-Matrix and Cell-Cell Interactions

Book series: Biology of Extracellular Matrix
Editors: Donald Gullberg & Johannes A. Eble
Series Editor: Nikos K. Karamanos

About this book: Integrins are heterodimeric cell surface receptors which anchor cells to different extracellular matrix proteins or act as cell-cell receptors. They play pivotal roles not only across a wide range of physiological processes including tissue morphogenesis, wound healing, and regulation of cell growth, but also in numerous pathological conditions such as autoimmunity, infectious disease, and carcinogenesis.

This book aims to provide readers a summary of the most important integrins and their respective biological functions. Readers will learn about knockout- and animal models to study the functionality

of key collagen-, laminin-, and nephronectin-binding integrins. Additionally, the role of integrins in pathological tissue remodeling in joints and in developing and diseased cardiac tissue are discussed. Reviews of the current knowledge of the role of integrins in tissue and tumor fibrosis, angiogenesis and tumor progression are an important part of this work. Finally, the book discusses integrins in the context of the immune system, how to target integrin-ligand interactions with antibodies, and the role of integrins as receptors for bacterial and viral cell invasion.

Both experienced researchers and clinicians, as well as PhD students who wish to study the extracellular matrix and cell adhesion molecules will find "Integrins in Health and Disease - Key Effectors of Cell-Matrix and Cell-Cell Interactions" authoritative, easily accessible, and vastly informative.

The series *Biology of Extracellular Matrix* is published in collaboration with the American Society for Matrix Biology and the International Society for Matrix Biology.

Research networks

European commission funds multinational project on heparanase inhibitors in cancer treatment: the HEPINIB project

January 2023 marked the starting point of a joint project of ECM experts and industry partners on the development and evaluation of heparanase inhibitors as a multitargeting approach for cancer treatment. Called HEPINIB, and led by coordinator Martin Götte from Münster, Germany, this European Comission-funded project of the Marie Skłodowska-Curie Actions program involves exchanges of scientists between academic and industry teams from Haifa, Milan, Reims, Uppsala, Bonn, Tartu and Buenos Aires.

Heparanase - the sole HS degrading endoglycosidase, regulates multiple biological activities that enhance tumor growth, metastasis, angiogenesis and inflammation. The joint scientific agenda includes a systematic testing of the hypothesis that heparanase constitutes an excellent drug target for cancer treatment. HEPINIB predicts that therapeutic targeting of HPSE is superior to conventional approaches, as it does not only have the potential to synchronously targeting tumor progression and metastasis at multiple levels (metastasis, angiogenesis, inflammation & immunity), but it is also expected to have a favourable side effects profile.

HEPINIB combines several prominent teams of the ECM community, including Israel Vlodavsky, Karin Forsberg-Nilsson, Stephane Brezillon, Laura Alaniz and the Ronzoni Institute. It is coordinated by Martin Götte (Martin.Goette@ukmuenster.de), Westfaelische Wilhelms University, Münster (Germany).

More information on the 4-year project can be found here: https://cordis.europa.eu/project/id/101086322

The ECMage (Extracellular Matrix (ECM) ageing across the life course interdisciplinary research) network

The ECMage (Extracellular Matrix (ECM) ageing across the life course interdisciplinary research) network is one of 11 UK Research and Innovation (UKRI)-Funded networks forming the UK Ageing Networks https://www.ukanet.org.uk/.
The ECMage network brings together complementary expertise in key aspects of ageing, matrix biology, chronobiology, AI/computational modelling and tissue engineering to develop novel models to study ECM ageing, particularly 3D biological models, new biomaterials to mimic tissue-specific ECM and models to predict novel anti-ageing therapies. Working together, sharing models, technologies, knowledge and expertise, we will strategically address challenges in ageing research with a view to generate paradigm-shifting discoveries with long-term benefit of improving lives and outcomes for older people.

Further details about our network, funding and events can be found on our website:
https://www.ukanet.org.uk/ecmage/ or email us at ecmage@liverpool.ac.uk

To join the ECMage Network please complete the form https://forms.office.com/e/rkEDP22TaD

International travel grants

ISMB provides international travel grants (on average 500 Euros) for young scientists (graduate students or postdocs up to 5 years after Ph.D., with extensions for maternity leave, military service, etc) 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.

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 will be paid out in the form of reimbursement to grant awardees, after reception of proof of participation. To this aim, users must send a receipt of the expenses (e.g., meeting subscription fees, etc.) within 3 months from the end of the meeting they received support for.

To apply for a travel grant, please fill the the form available on ISMB web site (https://www.ismb.org/copy-of-travel-grants) and append 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

Meeting reports from ISMB International Travel Awardees

2023 Cartilage Biology and Pathology Gordon Research Seminar and Conference Lucca, Italy, March 2023

I am a highly dedicated student and always try to develop myself through workshops, lectures and conferences as part of my PhD. Therefore, I was particularly pleased to win the international travel grant from ISMB. This award supported my attendance at the Gordon Research Seminar and Conference about Cartilage Biology and Pathology in March 2023.

As part of my doctoral studies, I am analyzing the influence of the sympathetic and parasympathetic nervous system on osteoarthritis and the conference empowered me to make significant progress towards understanding cartilage biology. All conference attendees were working on osteoarthritis, but investigated different aspects of the disease. The speakers talked about different models ranging from in vivo experiments to experimental setups in vitro with 2D and 3D techniques, including scaffolds, bioreactors, and chondrocytes on a chip. Because human cartilage is prone to disease and difficult to repair, we need to learn from other species, and therefore, cartilage from sharks to elephants has been studied. When a question was too complex to solve in one of these models, it was investigated via computer modelling. The aim of this conference was to bring all this knowledge together and to target osteoarthritis out of the box and get closer to a future therapy.

The GRC is a premier, international scientific conference focused on advancing the frontiers of science through the presentation of cutting-edge and unpublished research. This event was the perfect opportunity to present my newest unpublished data to an audience of scientists across disciplines. During the course of my talk and my poster presentation, I received a lot of valuable feedback to broaden the scope of my work and refine its quality. Several diverse and lively discussions opened new perspectives on my research and allowed me to take new project ideas to the next level.

The seminar and conference together lasted five days long and were held in a remote location in Italy to create scientific communities and foster lasting collaborations. During the seminar, I had the opportunity to exchange ideas with international PhD students from other institutes around the world about our research field, new ideas and future perspectives. Moreover, the conference offered the opportunity to position myself as new investigator in an environment of established scientists. I am convinced that the new contacts established at the seminar and the conference will form the basis for future innovative collaborations.

I am very grateful to have been able to attend Cartilage Biology and Pathology Gordon Research Seminar and Conference 2023, and I am convinced that I will continue to benefit from this valuable experience in my future scientific career.

Rebecca Sohn
Dr. Rolf M. Schwiete Research Unit for Osteoarthritis
University Hospital Frankfurt, Department of Orthopaedics (Friedrichsheim)
Frankfurt am Main, Germany

2023 Cartilage Biology and Pathology Gordon Research Seminar and Conference Lucca, Italy, March 2023

As a PhD student of the Dr. Rolf M. Schwiete Research Group for Osteoarthritis at the University Hospital Frankfurt, the ISMB Travel Grant enabled me to attend the Gordon Research Conference "Cartilage Biology and Pathology" in Luca, Italy. A part of my dissertation is a current study investigating the influence of chronic stress on the pathogenesis of OA in a mouse model. I have only recently obtained the first results from this study and was given the opportunity to present and discuss them in the form of a poster.

Overall, the GRC was an incredible experience. The conference brought together experts from around the world to discuss the latest research and developments in cartilage biology and pathology regardless of their career stage in science. A great advantage of the GRC is that new and unpublished data can be presented there safely and discussed afterwards. That is what makes the conference so valuable.

Other highlights of the conference were the keynote lectures, which covered a wide range of topics, including the role of stem cells in cartilage regeneration, the molecular mechanisms of cartilage development and homeostasis, and the pathophysiology of osteoarthritis and other cartilage-related diseases. The speakers were all highly knowledgeable and engaging, and their presentations provided valuable insights into the field.

The poster sessions were also a great opportunity to learn about ongoing research in the field. There were posters covering a wide variety of research including: novel biomaterials for cartilage repair, the use of imaging techniques in cartilage research, and the development of new therapies for cartilage-related disorders. It was exciting to see the various approaches being taken to address these complex issues.

Another great feature of the conference was the opportunity to meet and network with other researchers and clinicians. I had the chance to meet and chat with scientists from all over the world, exchange ideas and discuss potential collaborations. It was inspiring to see the level of passion and dedication among the attendees, and it left me feeling inspired and motivated to continue my own research in this area.

Overall, attending the GRC was an incredible experience that broadened my knowledge of the field and provided valuable networking opportunities. I look forward to attending future conferences and continuing to contribute to the advancement of cartilage research.

Many thanks to ISMB for their support!

Gundula Rösch
Dr. Rolf M. Schwiete Research Unit for Osteoarthritis
Department of Orthopedics (Friedrichsheim)
University Hospital Frankfurt, Goethe University,
Frankfurt / Main

Recent publications

Fibrillin microfibril structure identifies long-range effects of inherited pathogenic mutations affecting a key regulatory latent TGFβ-binding site. Godwin ARF, Dajani R, Zhang X, Thomson J, Holmes DF, Adamo CS, Sengle G, Sherratt MJ, Roseman AM, Baldock C. Nat Struct Mol Biol. 2023 Apr 20. doi: 10.1038/s41594-023-00950-8
Corresponding author: clair.baldock@manchester.ac.uk
Abstract: *Genetic mutations in fibrillin microfibrils cause serious inherited diseases, such as Marfan syndrome and Weill-Marchesani syndrome (WMS). These diseases typically show major dysregulation of tissue development and growth, particularly in skeletal long bones, but links between the mutations and the diseases are unknown. Here we describe a detailed structural analysis of native fibrillin microfibrils from mammalian tissue by cryogenic electron microscopy. The major bead region showed pseudo eightfold symmetry where the amino and carboxy termini reside. On the basis of this structure, we show that a WMS deletion mutation leads to the induction of a structural rearrangement that blocks interaction with latent TGFβ-binding protein-1 at a remote site. Separate deletion of this binding site resulted in the assembly of shorter fibrillin microfibrils with structural alterations. The integrin αvβ3-binding site was also mapped onto the microfibril structure. These results establish that in complex extracellular assemblies, such as fibrillin microfibrils, mutations may have long-range structural consequences leading to the disruption of growth factor signaling and the development of disease.*

How the mechanobiology orchestrates the iterative and reciprocal ECM-cell crosstalk that drives microtissue growth. Benn MC, Pot SA, Moeller J, Yamashita T, Fonta CM, Orend G, Kollmannsberger P, Vogel V. Science Advances, 9(13), eadd9275 (2023).
Corresponding authors: viola.vogel@hest.ethz.ch and mario.benn@hest.etzh.ch
Abstract: *Controlled tissue growth is essential for multicellular life and requires tight spatiotemporal control over cell proliferation and differentiation until reaching homeostasis. As cells synthesize and remodel extracellular matrix, tissue growth processes can only be understood if the reciprocal feedback between cells and their environment is revealed. Using de novo-grown microtissues, we identified crucial actors of the mechanoregulated events, which iteratively orchestrate a sharp transition from tissue growth to maturation, requiring a myofibroblast-to-fibroblast transition. Cellular decision-making occurs when fibronectin fiber tension switches from highly stretched to relaxed, and it requires the transiently up-regulated appearance of tenascin-C and tissue transglutaminase, matrix metalloprotease activity, as well as a switch from α5β1 to α2β1 integrin engagement and epidermal growth factor receptor signaling. As myofibroblasts are associated with wound healing and inflammatory or fibrotic diseases, crucial knowledge needed to advance regenerative strategies or to counter fibrosis and cancer progression has been gained.*

Infiltrating CD8+ T cells and M2 macrophages are retained in tumor matrix tracks enriched in low tension fibronectin fibers.
Fonta CM, Loustau T, Li C, Poilil Surendran S, Hansen U, Murdamoothoo D, Benn MC, Velazquez-Quesada I, Carapito R, Orend G, Vogel V. Matrix Biol. 2023 Feb;116:1-27.
Corresponding author: viola.vogel@hest.ethz.ch
Abstract: *Tracks rich in matrix and cells, as described in several cancer types, have immunosuppressive functions and separate tumor nests and stroma, yet their origin is unknown. Immunostainings of cryosections from mouse breast tumors show that these tracks are bordered by an endothelial-like basement membrane, filled with fibers of collagen adjacent to tenascin-C (TNC) and low-tension fibronectin (Fn) fibers. While present in early-stage tumors and maturing with time, tracks still form under TNC KO conditions, however, host (not tumor cell)-derived*

TNC is important for track maturation. Tumor infiltrating leukocytes (mostly M2 macrophages and CD8+ T cells) are retained in tracks of early-stage tumors. Following track maturation, retained tumor infiltrating leukocyte (TIL) numbers get reduced and more CD8+ TIL enter the tumor nests in the absence of TNC. As these tracks are enriched with platelets and fibrinogen and have a demarcating endothelial-like basement membrane often adjacent to endothelial cells, this suggests a role of blood vessels in the formation of these tracks. The Fn fiber tension probe FnBPA5 colocalizes with TNC and immune cells in the tracks and shows decreased binding in tracks lacking TNC. Consequently, FnBPA5 can serve as probe for tumor matrix tracks that have immune suppressive properties.
https://ethz.ch/en/news-and-events/eth-news/news/2023/03/how-tumours-transform-blood-vessels.html

Dissecting aortic aneurysm in Marfan syndrome is associated with losartan-sensitive transcriptomic modulation of aortic cells
Sun Y, Asano K, Sedes L, Cantalupo A, Hansen J, Iyengar R , Walsh MJ, Ramirez F. JCI Insight 2023 Apr 6;e168793. doi: 10.1172/jci.insight.168793.
Corresponding author: francesco.ramirez@mssm.edu
Abstract: *To improve our limited understanding of the pathogenesis of thoracic aortic aneurysm (TAA) leading to acute aortic dissection, single-cell RNA sequencing (scRNA-seq) was employed to profile disease-relevant transcriptomic changes of aortic cell populations in a well-characterized mouse model of the most commonly diagnosed form of Marfan syndrome (MFS). As result, two discrete sub-populations of aortic cells (SMC3 and EC4) were identified only in the aorta of Fbn1mgR/mgR mice. SMC3 highly express genes related to extracellular matrix formation and nitric oxide signaling, whereas EC4 transcriptional profile is enriched in SMC, fibroblast, and immune cell-related genes. Trajectory analysis predicted close phenotypic modulation between SMC3 and EC4, which were therefore analyzed together as a discrete MFS-modulated (MFSmod) sub-population. In situ hybridizations of diagnostic transcripts located MFSmod cells to the intima of Fbn1mgR/mgR aortas. Reference-based dataset integration revealed transcriptomic similarity between MFSmod and an SMC-derived cell cluster modulated in human TAA. Consistent with angiotensin II type I receptor (At1r) contribution to TAA development, MFSmod cells were absent in the aorta of Fbn1mgR/mgR mice treated with the At1r antagonist losartan. Altogether, our findings indicate that a discrete dynamic alteration of aortic cell identity is associated with dissecting TAA in MFS mice and increased risk of aortic dissection in MFS patients.*

Conditional expression of endorepellin in the tumor vasculature attenuates breast cancer growth, angiogenesis and hyaluronan deposition. Chen CG, Kapoor A, Xie C, Moss A, Vadigepalli R, Ricard-Blum S, Iozzo RV. Matrix Biol. 2023 118:92-109. PMID: 36907428
Corresponding author: Renato.Iozzo@jefferson.edu
Abstract: *The tumor stroma of most solid malignancies is characterized by a pathological accumulation of pro-angiogenic and pro-tumorigenic hyaluronan driving tumorigenesis and metastatic potential. Of all three hyaluronan synthase isoforms, HAS2 is the primary enzyme that promotes the build-up of tumorigenic HA in breast cancer. Previously, we discovered that endorepellin, the angiostatic C-terminal fragment of perlecan, evokes a catabolic mechanism targeting endothelial HAS2 and hyaluronan via autophagic induction. To explore the translational implications of endorepellin in breast cancer, we created a double transgenic, inducible Tie2CreERT2;endorepellin(ER)Ki mouse line that expresses recombinant endorepellin specifically from the endothelium. We investigated the therapeutic effects of recombinant endorepellin overexpression in an orthotopic, syngeneic breast cancer allograft mouse model. First, adenoviral delivery of Cre evoking intratumor expression of endorepellin in ERKi mice suppressed breast cancer growth, peritumor hyaluronan and angiogenesis. Moreover, tamoxifen-induced expression of recombinant endorepellin specifically from the endothelium in Tie2CreERT2;ERKi mice markedly suppressed breast cancer allograft growth, hyaluronan deposition in the tumor*

proper and perivascular tissues, and tumor angiogenesis. These results provide insight into the tumor suppressing activity of endorepellin at the molecular level and implicate endorepellin as a promising cancer protein therapy that targets hyaluronan in the tumor microenvironment.

The C-terminal domains of ADAMTS1 contain exosites involved in its proteoglycanase activity
Minns AF, Qi Y, Yamamoto K, Lee K, Ahnström J, Santamaria S. J Biol Chem 2023 Feb 21;299(4):103048.
Corresponding author: s.santamaria@surrey.ac.uk
Abstract: *A disintegrin-like and metalloproteinase with thrombospondin type 1 motifs (ADAMTS1) is a protease involved in fertilization, cancer, cardiovascular development, and thoracic aneurysms. Proteoglycans such as versican and aggrecan have been identified as ADAMTS1 substrates, and Adamts1 ablation in mice typically results in versican accumulation; however, previous qualitative studies have suggested that ADAMTS1 proteoglycanase activity is weaker than that of other family members such as ADAMTS4 and ADAMTS5. Here, we investigated the functional determinants of ADAMTS1 proteoglycanase activity. We found that ADAMTS1 versicanase activity is approximately 1000-fold lower than ADAMTS5 and 50-fold lower than ADAMTS4 with a kinetic constant (kcat/Km) of 3.6 × 103 M-1 s-1 against full-length versican. Studies on domain-deletion variants identified the spacer and cysteine-rich domains as major determinants of ADAMTS1 versicanase activity. Additionally, we confirmed that these C-terminal domains are involved in the proteolysis of aggrecan as well as biglycan, a small leucine-rich proteoglycan. Glutamine scanning mutagenesis of exposed positively charged residues on the spacer domain loops and loop substitution with ADAMTS4 identified clusters of substrate-binding residues (exosites) in β3-β4 (R756Q/R759Q/R762Q), β9-β10 (residues 828-835), and β6-β7 (K795Q) loops. This study provides a mechanistic foundation for understanding the interactions between ADAMTS1 and its proteoglycan substrates and paves the way for development of selective exosite modulators of ADAMTS1 proteoglycanase activity.*

Mesenchyme-derived vertebrate lonesome kinase controls lung organogenesis by altering the matrisome.
Brütsch SM, Madzharova E, Pantasis S, Wüstemann T, Gurri S, Steenbock H, Gazdhar A, Kuhn G, Angel P, Bellusci S, Brinckmann J, Auf dem Keller U, Werner S, Bordoli MR. Cell Mol Life Sci. 2023 80, 89. PMID: 36920550.
Corresponding authors: uadk@dtu.dk, sabine.werner@biol.ethz.ch and mattia.bordoli@novartis.com
Abstract: *Vertebrate lonesome kinase (VLK) is the only known secreted tyrosine kinase and responsible for the phosphorylation of a broad range of secretory pathway-resident and extracellular matrix proteins. However, its cell-type specific functions in vivo are still largely unknown. Therefore, we generated mice lacking the VLK gene (protein kinase domain containing, cytoplasmic (Pkdcc)) in mesenchymal cells. Most of the homozygous mice died shortly after birth, most likely as a consequence of their lung abnormalities and consequent respiratory failure. E18.5 embryonic lungs showed a reduction of alveolar type II cells, smaller bronchi, and an increased lung tissue density. Global mass spectrometry-based quantitative proteomics identified 97 proteins with significantly and at least 1.5-fold differential abundance between genotypes. Twenty-five of these had been assigned to the extracellular region and 15 to the mouse matrisome. Specifically, fibromodulin and matrilin-4, which are involved in extracellular matrix organization, were significantly more abundant in lungs from Pkdcc knockout embryos. These results support a role for mesenchyme-derived VLK in lung development through regulation of matrix dynamics and the resulting modulation of alveolar epithelial cell differentiation*

Recreating the extracellular matrix: novel 3D cell culture platforms in cancer research.
Kyriakopoulou K, Koutsakis C, Piperigkou Z, Karamanos NK (2023) FEBS J. doi: 10.1111/febs.16778.
Corresponding author: n.k.karamanos@upatras.gr

Abstract: *Cancer initiation and progression heavily rely on microenvironmental cues derived from various components of the niche including the extracellular matrix (ECM). Although the 2D cell culture systems provide useful information at the molecular level and preclinical testing, they could not accurately represent the in vivo matrix microenvironmental architecture. Hence, it is no surprise that researchers in the last decade have focused their efforts on establishing novel advanced in vitro culture models that mimic tumour and tissue-specific niches and interactions. These numerous 3D culture systems that are now widely available, as well as those still under development, grant researchers with new, improved tools to study cancer progression and to explore innovative therapeutic options. Herein, we report on the emerging methods and cutting-edge technologies in 3D cell culture platforms and discuss their potential use in unveiling tumour microenvironmental cues, drug screening and personalized treatment.*

The Role of Exosomes in Epithelial-to-Mesenchymal Transition and Cell Functional Properties in Head and Neck Cancer. Mastronikolis NS, Kyrodimos E, Spyropoulou D, Delides A, Giotakis E, Piperigkou Z, Karamanos NK (2023) Cancers 15(7), 2156; doi: 10.3390/cancers15072156

Corresponding author: n.k.karamanos@upatras.gr

Abstract: *According to WHO 2018 estimates, cancer is the second leading cause of mortality worldwide after cardiovascular disease, accounting for one in six fatalities. Mortality due to head and neck cancer is also significantly high, making it the seventh most prevalent cancer. Elucidating the mechanisms of action of key regulators, such as bioactive molecules secreted by the cancer cells in exosomes, their interaction with neighboring and distant cells, the extracellular matrix, and the tumor microenvironment, could be a valuable tool for future diagnostic and treatment approaches. Exosomes facilitate several critical functions in cancer cells, such as epithelial-to-mesenchymal transition, which makes head and neck cancer even worse by giving it a metastatic potential to evade the secondary site and spread cancer in the body. Exploring the molecules involved in this process could help targeting specific sites, for instance, by modifying the cell-specific proteins and exosome cargoes.*

Phase-specific signatures of wound fibroblasts and matrix patterns define cancer-associated fibroblast subtypes.

Wietecha MS, Lauenstein D, Cangkrama M, Seiler S, Jin J, Goppelt A, Claassen M, Levesque MP, Dummer R, Werner S.

Matrix Biol. 2023 119, 19-56.

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Abstract: *Healing wounds and cancers present remarkable cellular and molecular parallels, but the specific roles of the healing phases are largely unknown. We developed a bioinformatics pipeline to identify genes and pathways that define distinct phases across the time-course of healing. Their comparison to cancer transcriptomes revealed that a resolution phase wound signature is associated with increased severity in skin cancer and enriches for extracellular matrix-related pathways. Comparisons of transcriptomes of early- and late-phase wound fibroblasts vs skin cancer-associated fibroblasts (CAFs) identified an "early wound" CAF subtype, which localizes to the inner tumor stroma and expresses collagen-related genes that are controlled by the RUNX2 transcription factor. A "late wound" CAF subtype localizes to the outer tumor stroma and expresses elastin-related genes. Matrix imaging of primary melanoma tissue microarrays validated these matrix signatures and identified collagen- vs elastin-rich niches within the tumor microenvironment, whose spatial organization predicts survival and recurrence. These results identify wound-regulated genes and matrix patterns with prognostic potential in skin cancer.*

Glycosaminoglycans: What Remains To Be Deciphered? Perez S, Makshakova O, Angulo J, Bedini E, Bisio A, de Paz JL, Fadda E, Guerrini M, Hricovini M, Hricovini M, Lisacek F, Nieto PM, Pagel K, Paiardi G, Richter R, Samsonov SA, Vivès RR, Nikitovic D, Ricard Blum S. JACS Au (2023) Mar 2;3(3):628-656.
Corresponding author: serge.perez@cermav.cnrs.fr
Abstract: *Glycosaminoglycans (GAGs) are complex polysaccharides exhibiting a vast structural diversity and fulfilling various functions mediated by thousands of interactions in the extracellular matrix, at the cell surface, and within the cells where they have been detected in the nucleus. It is known that the chemical groups attached to GAGs and GAG conformations comprise "glycocodes" that are not yet fully deciphered. The molecular context also matters for GAG structures and functions, and the influence of the structure and functions of the proteoglycan core proteins on sulfated GAGs and vice versa warrants further investigation. The lack of dedicated bioinformatic tools for mining GAG data sets contributes to a partial characterization of the structural and functional landscape and interactions of GAGs. These pending issues will benefit from the development of new approaches reviewed here, namely (i) the synthesis of GAG oligosaccharides to build large and diverse GAG libraries, (ii) GAG analysis and sequencing by mass spectrometry (e.g., ion mobility-mass spectrometry), gas-phase infrared spectroscopy, recognition tunnelling nanopores, and molecular modeling to identify bioactive GAG sequences, biophysical methods to investigate binding interfaces, and to expand our knowledge and understanding of glycocodes governing GAG molecular recognition, and (iii) artificial intelligence for in-depth investigation of GAGomic data sets and their integration with proteomics.*

Solvent models benchmark for molecular dynamics of glycosaminoglycans. Marcisz M., Samsonov S.A. *J Chem Inf Mod.* 2023. https://doi.org/10.1021/acs.jcim.2c01472
Corresponding authors: mateusz.marcisz@phdstud.ug.edu.pl and sergey.samsonov@ug.edu.pl
Abstract: *In computational studies of glycosaminoglycans (GAGs), a group of anionic, periodic linear polysaccharides, so far there has been very little discussion about the role of solvent models in the molecular dynamics simulations of these molecules. Predominantly, the TIP3P water model is commonly used as one of the most popular explicit water models in general. However, there are numerous alternative explicit and implicit water models that are neglected in the computational research of GAGs. Since solvent-mediated interactions are particularly important for GAG dynamic and structural properties, it would be of great interest for the GAG community to establish the solvent model that is suited the best in terms of the quality of theoretically obtained GAG parameters and, at the same time, would be reasonably demanding in terms of computational resources required. In this study, heparin (HP) was simulated using five implicit and six explicit solvent models with the aim to find out how different solvent models influence HP's molecular descriptors in the molecular dynamics simulations. Here, we initiate the search for the most appropriate solvent representation for GAG systems and we hope to encourage other groups to contribute to this highly relevant subject.*

Computational modeling of the molecular basis for the calcium-dependence of the mannuronan C-5 epimerase AvAlgE6 from *Azotobacter vinelandii*. Gaardløs M., Lervik A., Samsonov S.A. Computational and Structural Biotechnology Journal. 2023. 14:458-465. https://doi.org/10.1016/j.csbj.2023.03.021
Corresponding authors: margrethe.gaardlos@gmail.com and sergey.samsonov@ug.edu.pl
Abstract: *Furin is a human serine protease responsible for activating numerous physiologically relevant cell substrates and is also involved in the development of various pathological conditions, including inflammatory diseases, cancers, and viral and bacterial infections. Therefore, compounds with the ability to inhibit furin's proteolytic action are regarded as potential therapeutics. Here we took the combinatorial chemistry approach (library consisting of 2000 peptides) to obtain new, strong, and stable peptide furin inhibitors. The extensively studied trypsin inhibitor SFTI-1 was used as a leading structure. A selected monocylic inhibitor was further*

*modified to finally yield five mono- or bicyclic furin inhibitors with values of K_i in the subnanomolar range. Inhibitor **5** was the most active (K_i = 0.21 nM) and significantly more proteolytically resistant than the reference furin inhibitor described in the literature. Moreover, it reduced furin-like activity in PANC-1 cell lysate. Detailed analysis of furin–inhibitor complexes using molecular dynamics simulations is also reported.*

Molecular dynamics-based comparative analysis of chondroitin and dermatan sulfates. Pągielska M., Samsonov S.A Biomolecules. 2023. Vol. 13: 247. https://doi.org/10.3390/biom13020247
Corresponding author: sergey.samsonov@ug.edu.pl
Abstract: *Procathepsins, inactive precursors of cathepsins are present in the extracellular matrix (ECM) and in lysosomes. Their active forms are involved in a number of biologically relevant processes, including bone resorption, intracellular proteolysis and regulation of programmed cell death. These processes might be mediated by glycosaminoglycans (GAGs), long unbranched periodic negatively charged polysaccharides. GAGs are also present in ECM and play important role in anticoagulation, angiogenesis and tissue regeneration. GAGs not only mediate the enzymatic activity of cathepsins but can also regulate the process of procathepsin maturation, as it was shown for procathepsin B and S. In this study, we propose the molecular mechanism underlying the biological role of GAGs in procathepsin S maturation and compare our findings with computational data obtained for procathepsin B. We rigorously analyse procathepsin S–GAG complexes in terms of their dynamics, free energy and potential allosteric regulation. We conclude that the GAG binding region might have an effect on the dynamics of procathepsin S structure and so affect its maturation by two different mechanisms.*

Ten years of extracellular matrix proteomics: Accomplishments, challenges, and future perspectives. Naba A. Molecular and Cellular Proteomics, 2023, 12:100528. 10.1016/j.mcpro.2023.100528
Corresponding author: anaba@uic.edu
Abstract: *The extracellular matrix (ECM) is a complex assembly of hundreds of proteins forming the architectural scaffold of multicellular organisms. In addition to its structural role, the ECM conveys signals orchestrating cellular phenotypes. Alterations of ECM composition, abundance, structure, or mechanics have been linked to diseases and disorders affecting all physiological systems, including fibrosis and cancer. Deciphering the protein composition of the ECM and how it changes in pathophysiological contexts is thus the first step toward understanding the roles of the ECM in health and disease and toward the development of therapeutic strategies to correct disease-causing ECM alterations. Potentially, the ECM also represents a vast, yet untapped reservoir of disease biomarkers. ECM proteins are characterized by unique biochemical properties that have hindered their study: they are large, heavily and uniquely posttranslationally modified, and highly insoluble. Overcoming these challenges, we and others have devised mass-spectrometry-based proteomic approaches to define the ECM composition, or "matrisome," of tissues. This first part of this review provides a historical overview of ECM proteomics research and presents the latest advances that now allow the profiling of the ECM of healthy and diseased tissues. The second part highlights recent examples illustrating how ECM proteomics has emerged as a powerful discovery pipeline to identify prognostic cancer biomarkers. The third part discusses remaining challenges limiting our ability to translate findings to clinical application and proposes approaches to overcome them. Lastly, the review introduces readers to resources available to facilitate the interpretation of ECM proteomics datasets. The ECM was once thought to be impenetrable. Mass spectrometry-based proteomics has proven to be a powerful tool to decode the ECM. In light of the progress made over the past decade, there are reasons to believe that the in-depth exploration of the matrisome is within reach and that we may soon witness the first translational application of ECM proteomics.*

Hepatocellular carcinoma exhibiting intratumor fibrosis, expresses cancer-specific extracellular matrix remodeling and WNT/TGFb signatures, associated with poor outcome. Desert R, Chen W, Ge X, Viel R, Han H, Athavale D, Das S, Song Z, Lantvit D, Cano L, Naba A, Musso O, Nieto N. Hepatology, 2023. 10.1097/hep.0000000000000362

Corresponding author: nnieto@uic.edu

Abstract: *Background aims: Hepatocellular carcinoma (HCC), the third cause of cancer-related death, arises in the context of liver fibrosis (LF). Although HCC is generally poorly fibrogenic, some tumors harbor focal intratumor extracellular matrix (ECM) deposits, called fibrous nests. To date, the molecular composition and the clinical relevance of these ECM deposits has not been fully defined. Approach results: We performed quantitative matrisome analysis by tandem mass tags mass spectrometry (TMT-MS) in 20 human HCCs, with high- or low-grade intratumor fibrosis, and matched non-tumor (NT) tissues, as well as in 12 livers from mice treated with vehicle, CCl4 or diethylnitrosamine (DEN). We found 94 ECM proteins differentially abundant between high- and low-grade fibrous nests, including interstitial and basement membrane components, such as several collagens, glycoproteins, proteoglycans, enzymes involved in ECM stabilization and degradation, and growth factors. Pathway analysis revealed a metabolic switch in high-grade fibrosis, with enhanced glycolysis and decreased oxidative phosphorylation. Integrating our quantitative proteomics data with the transcriptomes from HCCs and NT livers (n = 2,285 samples), we identified a subgroup of fibrous nest HCCs, characterized by cancer-specific ECM remodeling, expression of the WNT/TGFB (S1) subclass signature, and poor patient outcome. Fibrous nest HCCs, abundantly expressed an 11 fibrous nest proteins' signature, associated with poor patient outcome, by multivariate Cox analysis, and validated by multiplex immunohistochemistry. Conclusion: Matrisome analysis highlighted cancer-specific ECM deposits, typical of the WNT/TGFB HCC subclass, associated with poor patient outcome. Hence, histological reporting of intratumor fibrosis in HCC is of clinical relevance.*

Hedgehog is relayed through dynamic heparan sulfate interactions to shape its gradient.
Gude F, Froese J, Manikowski D, Di Iorio D, Grad JN, Wegner S, Hoffmann D, Kennedy M, Richter RP, Steffes G, Grobe K. Nat Commun. 2023 Feb 10;14(1):758. doi: 10.1038/s41467-023-36450-y.

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Abstract: *Cellular differentiation is directly determined by concentration gradients of morphogens. As a central model for gradient formation during development, Hedgehog (Hh) morphogens spread away from their source to direct growth and pattern formation in Drosophila wing and eye discs. What is not known is how extracellular Hh spread is achieved and how it translates into precise gradients. Here we show that two separate binding areas located on opposite sides of the Hh molecule can interact directly and simultaneously with two heparan sulfate (HS) chains to temporarily cross-link the chains. Mutated Hh lacking one fully functional binding site still binds HS but shows reduced HS cross-linking. This, in turn, impairs Hhs ability to switch between both chains in vitro and results in striking Hh gradient hypomorphs in vivo. The speed and propensity of direct Hh switching between HS therefore shapes the Hh gradient, revealing a scalable design principle in morphogen-patterned tissues.*

The dynamic nature of netrin-1 and the structural basis for glycosaminoglycan fragment-induced filament formation. Meier M, Gupta M, Akgül S, McDougall M, Imhof T, Nikodemus D, Reuten R, Moya-Torres A, To V, Ferens F, Heide F, Padilla-Meier GP, Kukura P, Huang W, Gerisch B, Mörgelin M, Poole K, Antebi A, Koch M, Stetefeld J. Nat Commun. 2023 Mar 3;14(1):1226. doi: 10.1038/s41467-023-36692-w.

Corresponding authors: aantebi@age.mpg.de and manuel.koch@uni-koeln.de and jorg.stetefeld@umanitoba.ca

Abstract: *Netrin-1 is a bifunctional chemotropic guidance cue that plays key roles in diverse cellular processes including axon pathfinding, cell migration, adhesion, differentiation, and survival. Here, we present a molecular*

understanding of netrin-1 mediated interactions with glycosaminoglycan chains of diverse heparan sulfate proteoglycans (HSPGs) and short heparin oligosaccharides. Whereas interactions with HSPGs act as platform to co-localise netrin-1 close to the cell surface, heparin oligosaccharides have a significant impact on the highly dynamic behaviour of netrin-1. Remarkably, the monomer-dimer equilibrium of netrin-1 in solution is abolished in the presence of heparin oligosaccharides and replaced with highly hierarchical and distinct super assemblies leading to unique, yet unknown netrin-1 filament formation. In our integrated approach we provide a molecular mechanism for the filament assembly which opens fresh paths towards a molecular understanding of netrin-1 functions.

Raman microspectroscopy identifies fibrotic tissues in collagen-related disorders via deconvoluted collagen type I spectra. Becker L, Lu CE, Montes-Mojarro IA, Layland SL, Khalil S, Nsair A, Duffy GP, Fend F, Marzi J, Schenke-Layland K. Acta Biomater. 2023 Mar 16:S1742-7061(23)00150-2. doi: 10.1016/j.actbio.2023.03.016.
Corresponding author: katja.schenke-layland@uni-tuebingen.de
Abstract: *Fibrosis is a consequence of the pathological remodeling of extracellular matrix (ECM) structures in the connective tissue of an organ. It is often caused by chronic inflammation, which over time, progressively leads to an excess deposition of collagen type I (COL I) that replaces healthy tissue structures, in many cases leaving a stiff scar. Increasing fibrosis can lead to organ failure and death; therefore, developing methods that potentially allow real-time monitoring of early onset or progression of fibrosis are highly valuable. In this study, the ECM structures of diseased and healthy human tissue from multiple organs were investigated for the presence of fibrosis using routine histology and marker-independent Raman microspectroscopy and Raman imaging. Spectral deconvolution of COL I Raman spectra allowed the discrimination of fibrotic and non-fibrotic COL I fibers. Statistically significant differences were identified in the amide I region of the spectral subpeak at 1608 cm-1, which was deemed to be representative for structural changes in COL I fibers in all examined fibrotic tissues. Raman spectroscopy-based methods in combination with this newly discovered spectroscopic biomarker potentially offer a diagnostic approach to non-invasively track and monitor the progression of fibrosis. STATEMENT OF SIGNIFICANCE: Current diagnosis of fibrosis still relies on histopathological examination with invasive biopsy procedures. Although, several non-invasive imaging techniques such as positron emission tomography, single-photon emission computed tomography and second harmonic generation are gradually employed in preclinical or clinical studies, these techniques are limited in spatial resolution and the morphological interpretation highly relies on individual experience and knowledge. In this study, we propose a non-destructive technique, Raman microspectroscopy, to discriminate fibrotic changes of collagen type I based on a molecular biomarker. The changes of the secondary structure of collagen type I can be identified by spectral deconvolution, which potentially can provide an automatic diagnosis for fibrotic tissues in the clinical application.*

Aggrecan governs intervertebral discs development by providing critical mechanical cues of the extracellular matrix. Empere M, Wang X, Prein C, Aspberg A, Moser M, Oohashi T, Clausen-Schaumann H, Aszodi A, Alberton P. Front Bioeng Biotechnol. 2023 Mar 2;11:1128587. doi: 10.3389/fbioe.2023.1128587.
Corresponding author: Paolo.Alberton@med.uni-muenchen.de
Abstract*: Aggrecan (ACAN) is localized in the intervertebral disc (IVD) in unique compartment-specific patterns where it contributes to the tissue structure and mechanical function together with collagens. The extracellular matrix (ECM) of the IVD undergoes degenerative changes during aging, misuse or trauma, which inevitably alter the biochemical and biomechanical properties of the tissue. A deeper understanding of these processes can be achieved in genetically engineered mouse models, taking into account the multifaceted aspects of IVD development. In this study, we generated aggrecan insertion mutant mice (Acan iE5/iE5) by interrupting exon 5 coding for the G1 domain of ACAN, and analyzed the morphological and mechanical properties of the different*

IVD compartments during embryonic development. Western blotting using an antibody against the total core protein failed to detect ACAN in cartilage extracts, whereas immunohistochemistry by a G1-specific antibody showed weak signals in vertebral tissues of Acan iE5/iE5 mice. Homozygous mutant mice are perinatally lethal and characterized by short snout, cleft palate and disproportionate dwarfism. Whole-mount skeletal staining and μ-CT analysis of Acan iE5/iE5 mice at embryonic day 18.5 revealed compressed vertebral bodies with accelerated mineralization compared to wild type controls. In Acan iE5/iE5 mice, histochemical staining revealed collapsed extracellular matrix with negligible sulfated glycosaminoglycan content accompanied by a high cellular density. Collagen type II deposition was not impaired in the IVD of Acan iE5/iE5 mice, as shown by immunohistochemistry. Mutant mice developed a severe IVD phenotype with deformed nucleus pulposus and thinned cartilaginous endplates accompanied by a disrupted growth plate structure in the vertebral body. Atomic force microscopy (AFM) imaging demonstrated a denser collagen network with thinner fibrils in the mutant IVD zones compared to wild type. Nanoscale AFM indentation revealed bimodal stiffness distribution attributable to the softer proteoglycan moiety and harder collagenous fibrils of the wild type IVD ECM. In Acan iE5/iE5 mice, loss of aggrecan resulted in a marked shift of the Young's modulus to higher values in all IVD zones. In conclusion, we demonstrated that aggrecan is pivotal for the determination and maintenance of the proper stiffness of IVD and vertebral tissues, which in turn could play an essential role in providing developmental biomechanical cues.

The Fraser Complex Proteins (Frem1, Frem2, and Fras1) Can Form Anchoring Cords in the Absence of AMACO at the Dermal-Epidermal Junction of Mouse Skin. Esho T, Kobbe B, Tufa SF, Keene DR, Paulsson M, Wagener R. Int J Mol Sci. 2023 Apr 5;24(7):6782. doi: 10.3390/ijms24076782.
Corresponding author: raimund.wagener@uni-koeln.de
Abstract: *AMACO (VWA2 protein), secreted by epithelial cells, is strongly expressed at basement membranes when budding or invagination occurs in embryos. In skin, AMACO associates with proteins of the Fraser complex, which form anchoring cords. These, during development, temporally stabilize the dermal-epidermal junction, pending the formation of collagen VII-containing anchoring fibrils. Fraser syndrome in humans results if any of the core members of the Fraser complex (Fras1, Frem1, Frem2) are mutated. Fraser syndrome is characterized by subepidermal blistering, cryptophthalmos, and syndactyly. In an attempt to determine AMACO function, we generated and characterized AMACO-deficient mice. In contrast to Fraser complex mutant mice, AMACO-deficient animals lack an obvious phenotype. The mutually interdependent basement membrane deposition of the Fraser complex proteins, and the formation of anchoring cords, are not affected. Furthermore, hair follicle development in newborn AMACO-deficient mice showed no gross aberration. Surprisingly, it appears that, while AMACO is a component of the anchoring cords, it is not essential for their formation or function.*

The Use of Collagen-Based Materials in Bone Tissue Engineering.
Fan L, Ren Y, Emmert S, Vučković I, Stojanovic S, Najman S, Schnettler R, Barbeck M, Schenke-Layland K, Xiong X. Int J Mol Sci. 2023 Feb 13;24(4):3744. doi: 10.3390/ijms24043744.
Corresponding authors: katja.schenke-layland@nmi.de and xin.xiong@nmie.de
Abstract: *Synthetic bone substitute materials (BSMs) are becoming the general trend, replacing autologous grafting for bone tissue engineering (BTE) in orthopedic research and clinical practice. As the main component of bone matrix, collagen type I has played a critical role in the construction of ideal synthetic BSMs for decades. Significant strides have been made in the field of collagen research, including the exploration of various collagen types, structures, and sources, the optimization of preparation techniques, modification technologies, and the manufacture of various collagen-based materials. However, the poor mechanical properties, fast degradation, and lack of osteoconductive activity of collagen-based materials caused inefficient bone replacement and limited their translation into clinical reality. In the area of BTE, so far, attempts have focused on the preparation of*

collagen-based biomimetic BSMs, along with other inorganic materials and bioactive substances. By reviewing the approved products on the market, this manuscript updates the latest applications of collagen-based materials in bone regeneration and highlights the potential for further development in the field of BTE over the next ten years.

The Tissue Factor Pathway in Cancer: Overview and Role of Heparan Sulfate Proteoglycans.
Hassan N, Efing J, Kiesel L, Bendas G, Götte M. Cancers (Basel). 2023 Feb 28;15(5):1524. doi: 10.3390/cancers15051524.
Corresponding author: mgotte@uni-muenster.de
Abstract: *Historically, the only focus on tissue factor (TF) in clinical pathophysiology has been on its function as the initiation of the extrinsic coagulation cascade. This obsolete vessel-wall TF dogma is now being challenged by the findings that TF circulates throughout the body as a soluble form, a cell-associated protein, and a binding microparticle. Furthermore, it has been observed that TF is expressed by various cell types, including T-lymphocytes and platelets, and that certain pathological situations, such as chronic and acute inflammatory states, and cancer, may increase its expression and activity. Transmembrane G protein-coupled protease-activated receptors can be proteolytically cleaved by the TF:FVIIa complex that develops when TF binds to Factor VII (PARs). The TF:FVIIa complex can activate integrins, receptor tyrosine kinases (RTKs), and PARs in addition to PARs. Cancer cells use these signaling pathways to promote cell division, angiogenesis, metastasis, and the maintenance of cancer stem-like cells. Proteoglycans play a crucial role in the biochemical and mechanical properties of the cellular extracellular matrix, where they control cellular behavior via interacting with transmembrane receptors. For TFPI.fXa complexes, heparan sulfate proteoglycans (HSPGs) may serve as the primary receptor for uptake and degradation. The regulation of TF expression, TF signaling mechanisms, their pathogenic effects, and their therapeutic targeting in cancer are all covered in detail here.*

The Heparan Sulfate Proteoglycan Syndecan-1 Triggers Breast Cancer Cell-Induced Coagulability by Induced Expression of Tissue Factor.
Hassan N, Bückreiß N, Efing J, Schulz-Fincke M, König P, Greve B, Bendas G, Götte M. Cells. 2023 Mar 16;12(6):910. doi: 10.3390/cells12060910.
Corresponding author: mgotte@uni-muenster.de
Abstract: *Syndecan-1 (Sdc-1) upregulation is associated with poor prognosis in breast cancer. Sdc-1 knockdown results in reduced angiogenesis and the dysregulation of tissue factor (TF) pathway constituents. Here, we evaluate the regulatory mechanisms and functional consequences of the Sdc-1/TF-axis using Sdc-1 knockdown and overexpression approaches in MCF-7 and MDA-MB-231 breast cancer cells. Gene expression was analyzed by means of qPCR. Thrombin generation and cell migration were detected. Cell-cycle progression and apoptosis were investigated using flow cytometry. In MDA-MB-231 cells, IL6, IL8, VEGF, and IGFR-dependent signaling affected TF pathway expression depending on Sdc-1. Notably, Sdc-1 depletion and TF pathway inhibitor (TFPI) synergistically affected PTEN, MAPK, and STAT3 signaling. At the functional level, the antiproliferative and pro-apoptotic effects of TFPI depended on Sdc-1, whereas Sdc-1's modulation of cell motility was not affected by TFPI. Sdc-1 overexpression in MCF-7 and MDA-MB-231 cells led to increased TF expression, inducing a procoagulative phenotype, as indicated by the activation of human platelets and increased thrombin formation. A novel understanding of the functional interplay between Sdc-1 and the TF pathway may be compatible with the classical co-receptor role of Sdc-1 in cytokine signaling. This opens up the possibility of a new functional understanding, with Sdc-1 fostering coagulation and platelet communication as the key to the hematogenous metastatic spread of breast cancer cells.*

Terminal Complement Activation Is Induced by Factors Released from Endplate Tissue of Disc Degeneration Patients and Stimulates Expression of Catabolic Enzymes in Annulus Fibrosus Cells.
Kuhn A, Riegger J, Teixeira GQ, Huber-Lang M, Lambris JD, Neidlinger-Wilke C, Brenner RE. Cells. 2023 Mar 13;12(6):887. doi: 10.3390/cells12060887.
Corresponding author: rolf.brenner@uni-ulm.de
Abstract: *Terminal complement complex (TCC) deposition was identified in human degenerated discs. To clarify the role of terminal complement activation in disc degeneration (DD), we investigated respective activating mechanisms and cellular effects in annulus fibrosus (AF) cells. Isolated cells from human AF, nucleus pulposus (NP), and endplate (EP) were stimulated with human serum alone or with zymosan and treated with either the C3 inhibitor Cp40 or the C5 antibody eculizumab. Complement activation was determined via anaphylatoxin generation and TCC deposition detection. Thereby, induced catabolic effects were evaluated in cultured AF cells. Moreover, C5 cleavage under degenerative conditions in the presence of AF cells was assessed. Zymosan-induced anaphylatoxin generation and TCC deposition was significantly suppressed by both complement inhibitors. Zymosan induced gene expression of ADAMTS4, MMP1, and COX2. Whereas the C3 blockade attenuated the expression of ADAMTS4, the C5 blockade reduced the expression of ADAMTS4, MMP1, and COX2. Direct C5 cleavage was significantly enhanced by EP conditioned medium from DD patients and CTSD. These results indicate that terminal complement activation might be functionally involved in the progression of DD. Moreover, we found evidence that soluble factors secreted by degenerated EP tissue can mediate direct C5 cleavage, thereby contributing to complement activation in degenerated discs.*

Drosophila hedgehog signaling range and robustness depend on direct and sustained heparan sulfate interactions. Manikowski D, Steffes G, Froese J, Exner S, Ehring K, Gude F, Di Iorio D, Wegner SV, Grobe K. Front Mol Biosci. 2023 Feb 22;10:1130064. doi: 10.3389/fmolb.2023.1130064.
Corresponding author: kgrobe@uni-muenster.de
Abstract: *Morphogens determine cellular differentiation in many developing tissues in a concentration dependent manner. As a central model for gradient formation during animal development, Hedgehog (Hh) morphogens spread away from their source to direct growth and pattern formation in the Drosophila wing disc. Although heparan sulfate (HS) expression in the disc is essential for this process, it is not known whether HS regulates Hh signaling and spread in a direct or in an indirect manner. To answer this question, we systematically screened two composite Hh binding areas for HS in vitro and expressed mutated proteins in the Drosophila wing disc. We found that selectively impaired HS binding of the second site reduced Hh signaling close to the source and caused striking wing mispatterning phenotypes more distant from the source. These observations suggest that HS constrains Hh to the wing disc epithelium in a direct manner, and that interfering with this constriction converts Hh into freely diffusing forms with altered signaling ranges and impaired gradient robustness.*

A20 binding and inhibitor of nuclear factor kappa B (NF-κB)-1 (ABIN-1): a novel modulator of mitochondrial autophagy. Merline R, Rödig H, Zeng-Brouwers J, Poluzzi C, Tascher G, Michaelis J, Lopez-Mosqueda J, Rhiner A, Huber LS, Diehl V, Dikic I, Kögel D, Münch C, Wygrecka M, Schaefer L. Am J Physiol Cell Physiol. 2023 Feb 1;324(2):C339-C352. doi: 10.1152/ajpcell.00493.2022.
Corresponding author: schaefer@med.uni-frankfurt.de
Abstract: *A20 binding inhibitor of nuclear factor kappa B (NF-κB)-1 (ABIN-1), a polyubiquitin-binding protein, is a signal-induced autophagy receptor that attenuates NF-κB-mediated inflammation and cell death. The present study aimed to elucidate the potential role of ABIN-1 in mitophagy, a biological process whose outcome is decisive in diverse physiological and pathological settings. Microtubule-associated proteins 1A/1B light chain 3B-II (LC3B-II) was found to be in complex with ectopically expressed hemagglutinin (HA)-tagged-full length (FL)-ABIN-1.*

Bacterial expression of ABIN-1 and LC3A and LC3B showed direct binding of ABIN-1 to LC3 proteins, whereas mutations in the LC3-interacting region (LIR) 1 and 2 motifs of ABIN-1 abrogated ABIN-1/LC3B-II complex formation. Importantly, induction of autophagy in HeLa cells resulted in colocalization of ABIN-1 with LC3B-II in autophagosomes and with lysosomal-associated membrane protein 1 (LAMP-1) in autophagolysosomes, leading to degradation of ABIN-1 with p62. Interestingly, ABIN-1 was found to translocate to damaged mitochondria in HeLa-mCherry-Parkin transfected cells. In line with this observation, clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9)-mediated deletion of ABIN-1 significantly inhibited the degradation of the mitochondrial outer membrane proteins voltage-dependent anion-selective channel 1 (VDAC-1), mitofusin-2 (MFN2), and translocase of outer mitochondrial membrane (TOM)20. In addition, short interfering RNA (siRNA)-mediated knockdown of ABIN-1 significantly decreased lysosomal uptake of mitochondria in HeLa cells expressing mCherry-Parkin and the fluorescence reporter mt-mKEIMA. Collectively, our results identify ABIN-1 as a novel and selective mitochondrial autophagy regulator that promotes mitophagy, thereby adding a new player to the complex cellular machinery regulating mitochondrial homeostasis.

A Lamb1Dendra2 mouse model identifies basement-membrane-producing origins and dynamics in PyMT breast tumors. Morgner J, Bornes L, Hahn K, López-Iglesias C, Kroese L, Pritchard CEJ, Vennin C, Peters PJ, Huijbers I, van Rheenen J. Dev Cell. 2023 Apr 10;58(7):535-549.e5. doi: 10.1016/j.devcel.2023.02.017.
Corresponding authors: j.morgner@nki.nl and j.v.rheenen@nki.nl
Abstract: *The basement membrane (BM) around tumor lobes forms a barrier to prevent cancer cells from invading the surrounding tissue. Although myoepithelial cells are key producers of the healthy mammary epithelium BM, they are nearly absent in mammary tumors. To study the origin and dynamics of the BM, we developed and imaged a laminin beta1-Dendra2 mouse model. We show that the turnover of laminin beta1 is faster in the BMs that surround the tumor lobes than in the BMs that surround the healthy epithelium. Moreover,* we find that *epithelial cancer cells and tumor-infiltrating endothelial cells synthesize laminin beta1 and that this production is temporarily and locally heterogeneous, leading to local discontinuity of the BM laminin beta1. Collectively, our data draw a new paradigm for tumor BM turnover in which the disassembly happens at a constant rate, and a local misbalance of compensating production leads to reduction or even complete disappearance of the BM.*

Functional Loss of Terminal Complement Complex Protects Rabbits from Injury-Induced Osteoarthritis on Structural and Cellular Level. Riegger J, Joos H, Möhler V, Leucht F, Rading K, Kubisch C, Ignatius A, Huber-Lang M, Brenner RE. Biomolecules. 2023 Jan 22;13(2):216. doi: 10.3390/biom13020216.
Corresponding author: jana.riegger@uni-ulm.de
Abstract: *The terminal complement complex (TCC) has been described as a potential driver in the pathogenesis of posttraumatic osteoarthritis (PTOA). However, sublytic TCC deposition might also play a crucial role in bone development and regeneration. Therefore, we elucidated the effects of TCC on joint-related tissues using a rabbit PTOA model. In brief, a C6-deficient rabbit breed was characterized on genetic, protein, and functional levels. Anterior cruciate ligament transection (ACLT) was performed in C6-deficient (C6-/-) and C6-sufficient (C6+/-) rabbits. After eight weeks, the progression of PTOA was determined histologically. Moreover, the structure of the subchondral bone was evaluated by µCT analysis. C6 deficiency could be attributed to a homozygous 3.6 kb deletion within the C6 gene and subsequent loss of the C5b binding site. Serum from C6-/- animals revealed no hemolytic activity. After ACLT surgery, joints of C6-/- rabbits exhibited significantly lower OA scores, including reduced cartilage damage, hypocellularity, cluster formation, and osteophyte number, as well as lower chondrocyte apoptosis rates and synovial prostaglandin E2 levels. Moreover, ACLT surgery significantly decreased the trabecular number in the subchondral bone of C6-/- rabbits. Overall, the absence of TCC protected from injury-induced OA progression but had minor effects on the micro-structure of the subchondral bone.*

Obesity Is Associated with Distorted Proteoglycan Expression in Adipose Tissue. Meen AJ, Doncheva AI, Böttcher Y, Dankel SN, Hoffmann A, Blüher M, Fernø J, Mellgren G, Ghosh A, Sun W, Dong H, Noé F, Wolfrum C, Pejler G, Dalen KT, Kolset SO. Int J Mol Sci . 2023 24(8):6884. doi: 10.3390/ijms24086884.
Corresponding author: astri.j.meen@uit.no
Abstract: Proteoglycans are central components of the extracellular matrix (ECM) and binding partners for inflammatory chemokines. Morphological differences in the ECM and increased inflammation are prominent features of the white adipose tissues in patients with obesity. The impact of obesity and weight loss on the expression of specific proteoglycans in adipose tissue is not well known. This study aimed to investigate the relationship between adiposity and proteoglycan expression. We analyzed transcriptomic data from two human bariatric surgery cohorts. In addition, RT-qPCR was performed on adipose tissues from female and male mice fed a high-fat diet. Both visceral and subcutaneous adipose tissue depots were analyzed. Adipose mRNA expression of specific proteoglycans, proteoglycan biosynthetic enzymes, proteoglycan partner molecules, and other ECM-related proteins were altered in both human cohorts. We consistently observed more profound alterations in gene expression of ECM targets in the visceral adipose tissues after surgery (among others VCAN ($p = 0.000309$), OGN ($p = 0.000976$), GPC4 ($p = 0.00525$), COL1A1 ($p = 0.00221$)). Further, gene analyses in mice revealed sex differences in these two tissue compartments in obese mice. We suggest that adipose tissue repair is still in progress long after surgery, which may reflect challenges in remodeling increased adipose tissues. This study can provide the basis for more mechanistic studies on the role of proteoglycans in adipose tissues in obesity.

Meeting announcements

The International Society for Hyaluronan Sciences (ISHAS) meeting - Hyaluronan 2023 4-8 June 2023 at the Hilton Portland Downtown, Portland, Oregon, USA.

The meeting will consist of ten scientific sessions (below) as well as an opening session with the presentation of the coveted “Rooster Prize”, a welcome reception and a conference dinner cruise.

1. HA Metabolism and Synthesis
2. Biophysics and Structural Biology of HA
3. HA in Signaling and Cellular Biology
4. New Therapeutics and Biotechnological Applications of HA
5. HA in Tissue Engineering and Regenerative Medicine
6. HA in Neurobiology
7. HA in Viral Biology
8. HA in Cancer Biology
9. HA in Inflammation and Immunology
10. HA in Development and Aging

Registration will open Nov.15, 2022 and we encourage you to register as soon as possible. (https://ishas.org/ha-2023/event-registration/) and visit https://ishas.org/ha-2023-conference/overview to find more information

Crosstalk between the ECM and proteases from destruction to regeneration
June 20-23, 2023, Rehovot, Israel

https://conferences.weizmann.ac.il/ECM2023/

FEBS 2023 ADVANCED COURSE

European Society of Tissue Regeneration in Orthopaedics & Traumatology
3-5 July, 2023, Frankfurt (Germany)

More information can be found here: http://www.estrot.org/

BONE REGENERATION
Non-union, bone defects, bone voids, avascular necrosis. The role of stem cells, Scaffolds, Growth factors, Composite grafts, Physical stimulation

CARTILAGE REGENERATION
Matrices, scaffolds, chondrocyte re-implantation, biological response modifiers

NERVE AND MUSCLE REGENERATION
Latest advances

SOFT TISSUE RECONSTRUCTION
VAC devices, growth promoting factors
Artificial skin, composite flaps

FRACTURE RELATED INFECTIONS
Preventative strategies for bone infection
Modern treatment of osteomyelitis

SURGICAL TECHNIQUES TO IMPROVE OUTCOMES
Osteosynthesis, distraction, arthroplasty

2023 Collagen Gordon Research Seminar

July 8 - 9, 2023

Colby Sawyer College, New London, NH (USA)

Chairs: Delfien Syx & Jonathan A. Roth

https://www.grc.org/collagen-grs-conference/2023/

2023 Collagen Gordon Research Conference

July 9-14, 2023

Colby Sawyer College, New London, NH (USA)

Chair: Taina Pihlajaniemi

Vice Chair: Douglas B. Gould

https://www.grc.org/collagen-conference/2023/

Gordon Research Conferences
Frontiers of Science

Physiological and Disease Relevance and the Underlying Molecular Properties of Collagens

- Keynote Session: : ECM dynamics in development and disease
- Functional Effects and Translational Potential of Mutations in Collagens
- Collagen Transport, Turnover and Homeostasis
- Collagens and Related Molecules in Stem Cell Regulation
- Bioengineering and Materials Design
- Tumor Growth and Metastasis
- Collagens: Systems Approaches, Networks and Interactomes
- Fibrosis and Tissue Repair
- Musculoskeletal Development and Pathology

2023 Elastin, Elastic Fibers & Microfibrils Gordon Research Seminar

July 22 - 23, 2023

https://www.grc.org/elastin-elastic-fibers-and-microfibrils-grs-conference/2023/

2023 Elastin, Elastic Fibers & Microfibrils Gordon Research Conference

Southern New Hampshire University, Manchester, NH (USA)

https://www.grc.org/elastin-elastic-fibers-and-microfibrils-conference/2023/

7th National Matrix Biology Academic Conference of the Chinese Society of Matrix Biology, Lishui, Zhejiang Province, China, August 2023

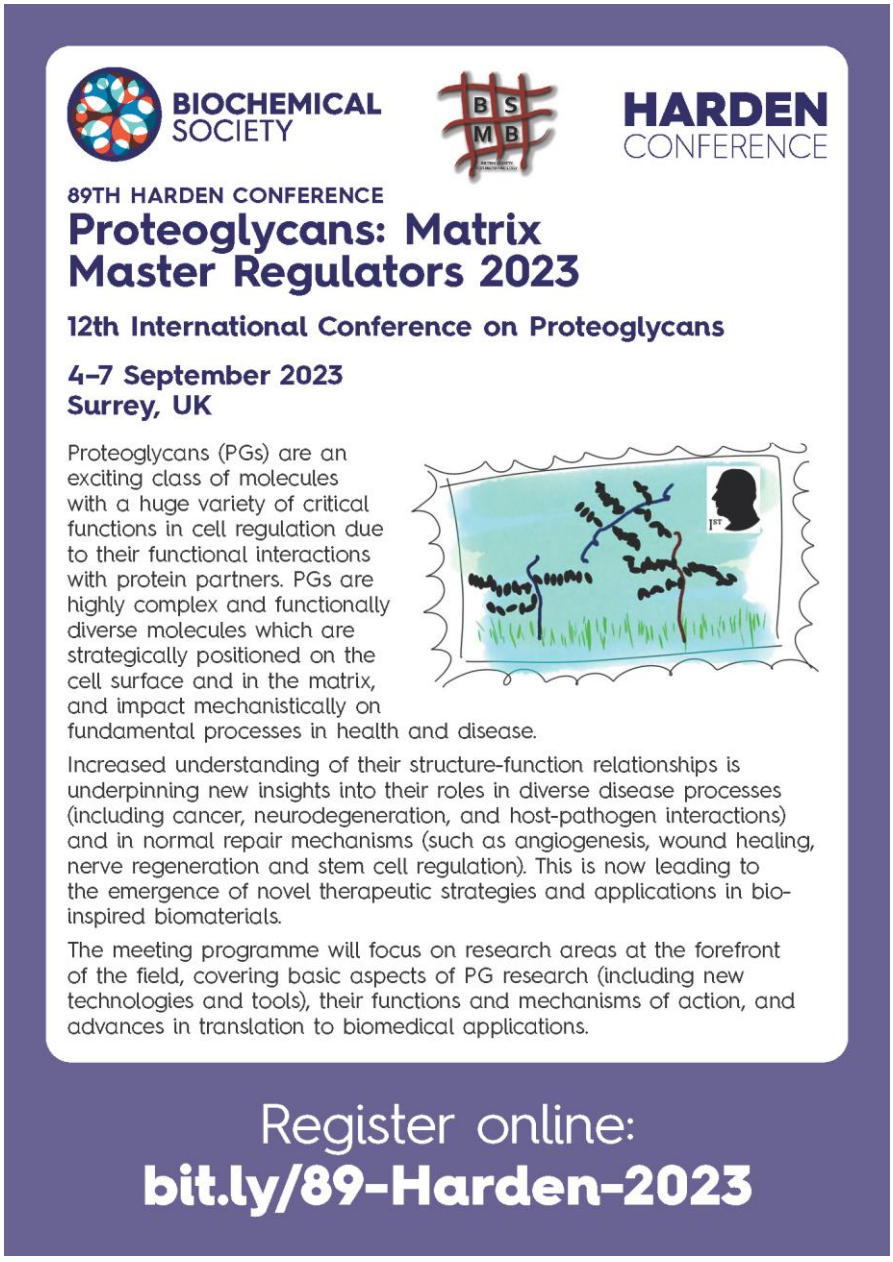
After discussion, the Committee of Chinese society of matrix biology (CSMB) plans to hold the 7th National Matrix Biology Academic Conference in **Lishui, Zhejiang Province, China**, in **August 2023**. The conference will discuss the matrix microenvironment and development, stem cell differentiation, transmembrane signal transduction, biomechanical characteristics and the relationship with tumors, bone joints, cardiovascular and other diseases from multiple perspectives. Lishui, known as Chuzhou in ancient times, is located in the southwest of Zhejiang Province, covering an area of 17300 square kilometers.

As its name implies, Lishui has incomparably beautiful landscapes. Lishui, with 3573 mountains above 1000 meters above sea level, is also the source of Oujiang River, Qiantang River, Minjiang River, Feiyun River, Lingjiang River and Fu'an River. Lishui is an excellent tourist city in China and a national civilized city. Nanjianyan, Huxian Palace, Baishanzu, Suichang National Mineral Park, etc. are all famous tourist attractions in Lishui. Lishui is also a famous city with profound cultural heritage. It is the first hometown of folk art in a prefecture level city in China, with rich historical and cultural relics. The famous Longquan celadon, Longquan sword and Qingtian stone carving are known as the "Three Treasures of Lishui". Welcome to Lishui, China.

89th Harden Conference Proteoglycans: Matrix Master Regulators 2023

4 - 7 September 2023 De Vere Horsley Estate, Surrey (UK)

https://www.eventsforce.net/biochemsoc/frontend/reg/thome.csp?pageID=76891&eventID=154



Additional information: **Space is limited to ~150 participants, so register early to avoid disappointment**. There will be ~40 short talks selected from Abstracts in the final programme. Accompanying persons fee for sharing a double/twin is £245 (including all meals). **The first 20 PhD students to register will receive a £100 reduction in registration fee**. Note that twin shared rooms are also available which will reduce costs by ~£195 for the shared room (details on the website).

Joint Annual Meeting of the German Society and Italian societies of Connective Tissues Münster (Germany) September 22-29, 2023

October 22-25, 2023 ASMB Biennial Meeting

Tissue, Matrix, and Pathobiology is an exciting new multidisciplinary and collaborative joint meeting of the American Society for Matrix Biology (ASMB), The Histochemical Society (HCS), and the American Society for Investigative Pathology (ASIP). The Program Committee has put together a fantastic four-day lineup of speakers, career sessions, workshops, and events - and can't wait to welcome you in Salt Lake City!

Who Should Attend:
Students, trainees, investigators, and educators who are working on cutting-edge basic, clinical, and translational research related to biology of cells and tissues, as well as molecular and cellular alterations that drive disease processes.

Scientific Programming
The scientific program includes award lectures, plenary sessions, symposia, and workshops featuring speakers who are leaders in their respective fields of study. Thematic highlights include:

- Extracellular Matrix Biology
- Liver Pathobiology
- Cardiovascular Diseases
- ECM Receptors
- Pathobiology of Fibrosis
- Cancer Pathobiology
- Matrix Disorders
- Neuropathology
- Organoid Models of Disease
- Mechanobiology
- Inflammatory and Infectious diseases
- Cell-Matrix Interactions

The meeting will also feature education and career development sessions that are focused on the needs of the current generation of trainees and young investigators. A generous scholar award program will provide travel grants for trainees and junior faculty who are members of the participating Societies. View the full program. https://asip2023.asip.org/program/joint-scientific-programs/

Matrix Biology Europe meeting 2024 Save the date!

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)

Membership
Suneel Apte (USA)

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

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

Twitter ISMB correspondents of National Societies for Matrix Biology

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
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
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The Danish Society for Matrix Biology (DSMB) Twitter @DSMB_dk
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The Finnish Connective Tissue Society (FSMB)
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