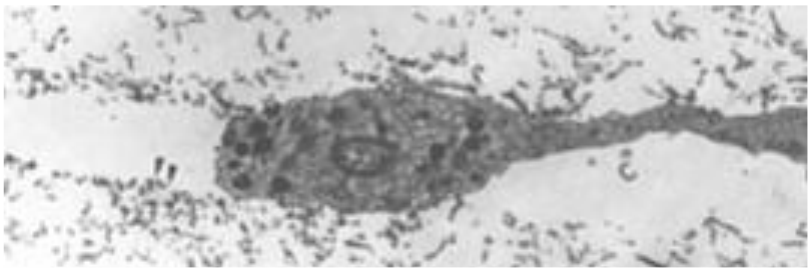

A fibroblast within a tethered lattice, after 13 days, with a cavity surrounding the cell and areas of packed collagen fibrils *(Porter et al. 1998 Wound Rep. Reg. 6: 157-166)*

ISMB NEWSLETTER 37 January 2021 Editor: Sylvie Ricard-Blum

FROM THE PAST-PRESIDENT AND THE PRESIDENT'S DESK

Dear ISMB members,

First of all, although we live in challenging and uncertain times, I wish you the very best for 2021 for in your personal and professional lives. Pandemic permitting, in-person meetings should resume this year if not this summer, at least this fall. Several major meetings with exciting scientific programs, thanks to their organizers, are planned for 2021 and are advertised in this newsletter. Although they could be postponed if the pandemic gets worse, it is important to keep them on our agenda.

My two-year term as President of the ISMB ended on December, 31st. It has been an honor and a pleasure to serve as President of our Society, and to work with the members of the Executive committee and the Council to support PhD students, post-doctoral fellows, and early-career investigators, and to promote the extracellular matrix field in close collaboration with Matrix Biology and Matrix Biology Plus journals, their Editor-in-Chief Renato Iozzo and Elsevier. The Society is in capable hands with the new President, Suneel Apte, and the new Vice-President, Nikos Karamanos. As Past-President I will be happy to continue to work with them and with the members of the Council. The Secretary of the ISMB, John Whitelock, will call soon for nominations for the Council vacancy with the requirement that the nominee must be based in Europe, and the Treasurer, Ruud Bank, will ask you to pay your membership fee, which is critical to support young scientists and meetings.

Let's stay optimistic and let's hope that we will meet in person in 2021. In the meantime, stay safe and well.

Best wishes.

Sylvie Ricard-Blum, Past-President of the ISMB (sylvie.ricard-blum@univ-lyon1.fr),

Dear Fellow Matrix Biologists:

Thanks are due to Sylvie for her 4 years commitment to ISMB, and especially for the time and effort she puts into the Newsletter as its Editor. It is a big task as you can imagine, but each issue is something to look forward to.

Sylvie will stay on as Past-President for another two years, so we will have continued access to her wisdom and decisiveness. Congratulations to Nikos Karamanos on his election as ISMB Vice-President. I know he will bring considerable enthusiasm and energy to ISMB. We are grateful to Ruud Bank, ISMB Treasurer, and Jo Adams and John Whitelock, past and current ISMB secretaries, whose roles are the most crucial, because they bring continuity to the Society. They are the ones who really hold the reins of the ISMB. We thank Valerio Izzi for taking on the role of first ISMB webmaster to keep our website up to date.

The light is visible at the end of the pandemic tunnel, we think, and there is a tinge of justified optimism to the in-person conference announcements in the newsletter. ISMB's mission is promoting matrix science and collaborations, and while the online format filled the gap for a while and may have even been received with enthusiasm by some, I have to be honest and say that I am zoomed out. Let's hope for a return, at least in large part, to what we prized so that ISMB can productively continue its important missions of promoting academic conferences, and the professional development of young scientists wishing to attend them. At the same time, the pandemic has shown that remote learning has its advantages too. Now it has become part of our shared global culture and is here to stay. Perhaps future conferences will have a "hybrid" format and perhaps rightly so, since not everyone can go to every relevant meeting each time.

Wish you all good health and a productive and enjoyable time in the lab.
Best wishes
Suneel Apte, President of the ISMB (aptes@ccf.org),

COMPOSITION OF ISMB COUNCIL SUBCOMMITTEES

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

Membership
Hide Watanabe (Japan)
Suneel Apte (USA)

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

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

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Valerio Izzi (Finland, Valerio.Izzi@oulu.fi)
Pauline Nauroy (Germany, pauline.nauroy@uniklinik-freiburg.de)
Chloé Yeung (Denmark, chloe.yeung@gmail.com)
The ISMB correspondents of National Societies for Matrix Biology for Facebook & Twitter

ISMB correspondents of National Societies for Matrix Biology for Facebook & Twitter

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

The Swiss Society for Matrix Biology (SSMB)
Collin Ewald, ETH Zurich (Switzerland)
collin-ewald@ethz.ch
Twitter of SSMB: @SwissMatrixBio

Matrix Biology World on Twitter

We are delighted to announce that 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**. We would be happy to share your announcements with the #MatrixBiology world!

Best paper award for Matrix Biology Plus

All the board members of Matrix Biology Plus picked their favorite paper and finally, **Dr. Yaqing Huang** and Dr. **Themis Kyriakides** won this prize with their article "**The role of extracellular matrix in the pathophysiology of diabetic wounds**."

Abstract: *Impaired healing leading to the formation of ulcerated wounds is a critical concern in patients with diabetes. Abnormalities in extracellular matrix (ECM) production and remodeling contribute to tissue dysfunction and delayed healing. Specifically, diabetes-induced changes in the expression and/or activity of structural proteins, ECM-modifying enzymes, proteoglycans, and matricellular proteins have been reported. In this review, we provide a summary of the key ECM molecules and associated changes in skin and diabetic wounds. Such information should allow for new insights in the understanding of impaired wound healing and lead to the development of ECM-based therapeutic strategies.*

This is announced on the journal homepages:
https://www.journals.elsevier.com/matrix-biology-plus/news/1st-matrix-biology-plus-best-paper-award
https://www.journals.elsevier.com/matrix-biology/news/1st-matrix-biology-plus-best-paper-award.

OBITUARIES

In the 68th year of his life, after a long illness, **Dr. Mátyás Mink**, associate professor, an employee of the Department of Medical Biology, Faculty of Medicine, University of Szeged, passed away on December 27, 2020

Dr. Mátyás Mink was born on July 2, 1952, in Mohács, Hungary. In 1976 he received a degree in chemistry from the University of Szeged, where he obtained a doctorate in 1980. He received his Candidate of Biological Sciences degree in 1992. Since 1995 he has been an associate professor at the University of Szeged. Throughout most of his professional career, he was connected to our University and the city of Szeged, but he worked abroad many times and enriched the Hungarian teaching, and research methodologies with the experience gained there.

He began his career at the Institute of Genetics of the Biological Research Center of the Hungarian Academy of Sciences, Szeged, as a doctoral student (1976-1979), then continued as a research fellow at the Department of Microbiology, Faculty of Science and Informatics, University of Szeged (1980-1989). From 1995 to 2015, he performed teaching and research duties at the Department of Genetics as an associate professor. From 2015, he was an employee of the Faculty of Medicine, Department of Medical Biology.

He began his work abroad in 1983: until 1985, he worked as a research fellow at the Max-Planck Institut in Göttingen. From 1989 to 1992, he was a lecturer at the University of Vienna (Universität Wien). He worked as a visiting professor for one year (1999-2000) at the American University of Hawai'i.

He was a member of several scientific societies, including the International Society for Matrix Biology. He devoted his life to the research of diseases caused by mutations in type IV collagen within the field of molecular genetics.

We preserve his memory with grace and carry on his legacy.
Dear Professor! Dear Matthias! Rest in peace!

András Attila Kiss
Department of Medical Biology
University of Szeged (Hungary)
kiss.andras.attila@gmail.com

Bryan Sykes: Matrix Biologist and Communicator

Professor Bryan Sykes, University of Oxford, died on 10th December 2020 at the age of 73.

Bryan Sykes began his research career in the 1970s as a biochemist at the University of Bristol, working on elastin and collagen under the guidance of Miles Partridge and Allen Bailey. After obtaining his PhD in 1973, he moved to Oxford where he worked with Martin Francis on hereditary matrix disorders. Among his early work, his most cited contribution was a method to separate collagens I and III from skin by interrupted gel electrophoresis. Soon after, he became a pioneer in DNA sequencing technology for the analysis of matrix proteins, notably in collaboration with Ellen Solomon on the first chromosomal assignment of a collagen gene (*Nature*, 1978). This was followed by the creation of the *Collagen Genetics Group* in Oxford which over the course of the next decades published a succession of key papers on the genetic basis of osteogenesis imperfecta, chondrodysplasias, Ehlers-Danlos and Marfans syndromes.

The year 1989 marked the beginning of a fundamental change in research directions, when Bryan and colleagues established a method for amplifying mitochondrial DNA from ancient bone samples over 5000 years old (Hagelberg E, Sykes B and Hedges R, *Nature*). This allowed him to pursue the use of DNA sequencing to trace human ancestry, as well as setting up the company *Oxford Ancestors*. There followed a string of highly cited publications on lineage tracing using mitochondrial DNA. This work also attracted the interest of the general public which allowed Bryan to show his outstanding skills as a scientific communicator. He wrote several books for a wide audience, including the bestseller *The Severn Daughters of Eve*, which revealed how the mitochondrial DNA of most Europeans could be traced to one of seven female lineages. Other books followed, on the future of the human Y chromosome, genetic roots of people in Britain and the USA, and why dogs are human's best friend. The latter involves Williams syndrome, hence a link to Bryan's early work on elastin.

Books by Bryan Sykes:
The Seven Daughters of Eve, Corgi, 2002, ISBN 978-0-552-14876-4
Adam's Curse, Bantam, 2003, ISBN 978-0-593-05004-0
Blood of the Isles, Bantam, 2006, ISBN 978-0-593-05652-3
DNA USA, W. W. Norton & Company, 2011, ISBN 978-0-393-07804-6
The Nature of the Beast, Hodder & Stoughton, 2015, ISBN 978-1-444-79126-6
Once a Wolf, Liveright, 2019, ISBN 978-1-63149-379-9

Further reading:
https://www.theguardian.com/science/2020/dec/18/bryan-sykes-obituary?CMP=share_btn_tw)
https://www.nytimes.com/2021/01/06/science/bryan-sykes-dead.html
https://www.labnews.co.uk/article/2024977/it_s_a_dog_s_life
https://en.wikipedia.org/wiki/Bryan_Sykes
British Matrix Biology Newsletter No. 98, January 2021

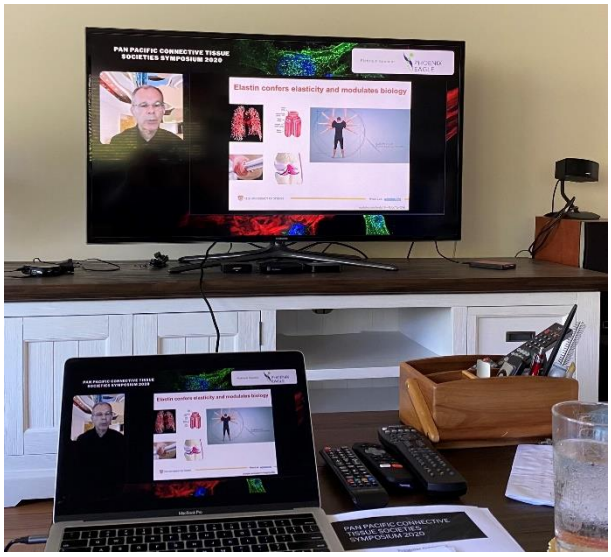
David Hulmes

MEETING REPORTS

PAN PACIFIC CONNECTIVE TISSUE SOCIETIES SYMPOSIUM 2020

Planning for the Pan Pacific Connective Tissue Societies Symposium 2020 commenced in the beginning of 2019. The meeting was to be held over 5 days November 2020 in Melbourne Australia, in conjunction with two local research societies, the Australasian Wound & Tissue Repair Society and the Matrix Biology Society of Australia and New Zealand. Organisation for the meeting was going as planned throughout 2019, and then 2020 rolled around, and the whole world changed!

The meeting organising committee looked at different scenarios for how we could hold the conference during the global pandemic, and it was decided that we did not want to postpone the meeting and that it would go ahead in a virtual format. In making this decision we knew that in holding a virtual meeting we were not going to be able to replicate all the elements that delegates would have had at a face-to-face meeting, but we did not want delegates to miss out on hearing all the scientific research that was occurring. Rather that write a report about the meeting I wanted to share the experience of holding a virtual meeting.

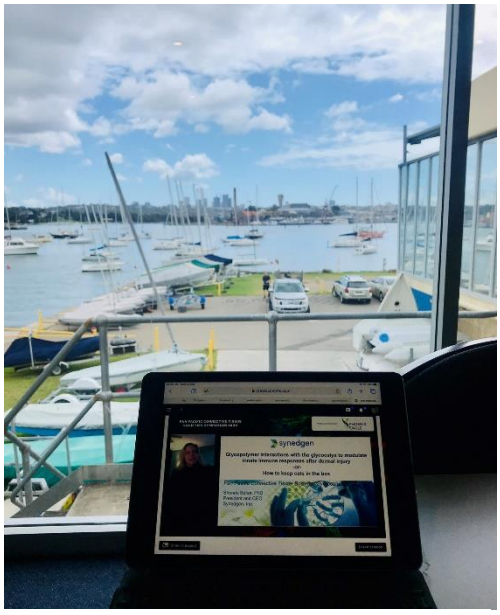


Here's my set up for #PPCTSS2020, everyone else just as comfortable and enjoying the great presentations? @MatrixBioANZ @IntSocMatBio (@HaupLarisa)

We decided to hold the meeting via a virtual conference platform, one of the main advantages of the platform was that all the presentations were recorded, and delegates were able to access the presentations for a month after the meeting was held. This was a great advantage especially for our international delegates where live presentation times might not have been convenient. Networking and social elements of the conference was going to be the hardest part to achieve, and a virtual platform would never truly recreate it. The conference platform allowed delegates to send messages and hold one-on-one video chats. An evening social activity was trivia, aimed at graduate research students and post-doctoral researchers as a way for them to meet new people in a more relaxed environment, which attendees really enjoyed. Rather than holding poster session we included Rapid Fire presentations in each scientific session, where presenters had 3 minutes to present and at the end of the presentations all of the Rapid Fire presenters for the session formed a panel for Q&As, which the delegates really enjoyed.

There was also a lot of activity on twitter during the meeting, search for #PPCTSS2020 to see all the posts (I've included some of the images).

Overall, the meeting was a success and we received lots of positive feedback. If you get the change to hold or attend a virtual meeting, I would highly recommend it, it is not going to be the same as a face-to-face meeting and it will be a worthwhile experience!



Another bonus of a virtual meeting, a room with a view! Fantastic science with a spectacular backdrop! #PPCTSS2020 @_AWTRS @MatrixBioANZ (@brookefarrugia)

Dr Brooke Farrugia
Pan Pacific Connective Tissue Societies Symposium 2020 Chair
President, Australasian Wound & Tissue Repair Society (AWTRS)
Secretary, Matrix Biology Society of Australia and New Zealand (MBSANZ)
Senior Lecturer, Department of Biomedical Engineering, The University of Melbourne, Australia
brooke.farrugia@unimelb.edu.au
twitter.com/brookefarrugia

The meeting was supported by the ISMB.

Rapid fire talk done! Now I can relax and enjoy the rest of the session and catch up on the previous ones too! #PPCTSS2020 (@ccstorytime)

Great Trivia night and networking by EMCRS at
#PPCTSS2020 virtual meeting can be fun and interactive!!
(@KopeckiZlatko)

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.

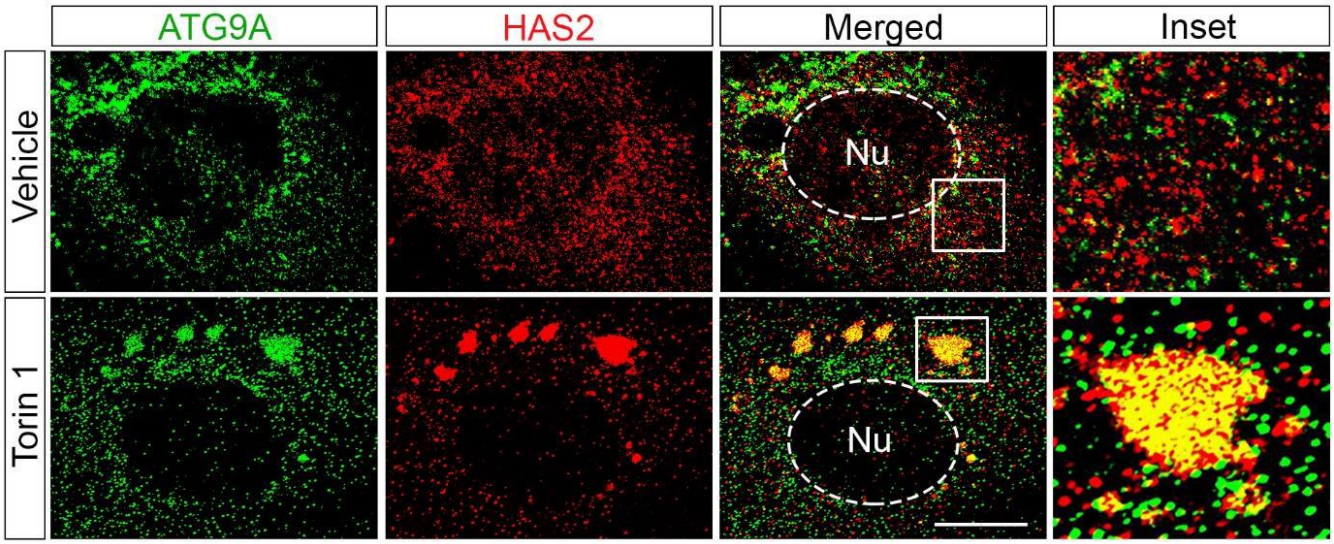
Every two years, the Society presents the Rupert Timpl Award to a young scientist (<40 years old), who is starting on their independent career, for the best paper related to matrix biology published in the previous two years and gives the Distinguished Investigator Award for lifetime achievement in the 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.

POSITIONS AVAILABLE

See also on ISMB website (http://ismb.org/career/)

Two NIH-funded postdoctoral fellowships in Dr. Iozzo's Lab
Thomas Jefferson University, Philadelphia PA

The positions require a Ph.D. and/or an M.D. and focus on the biology of two major proteoglycans: decorin and perlecan and their consequent effects on tumor angiogenesis, autophagy, stress signaling cascade, and mitophagy (1-7). The fellows will join an exciting and energetic team of researchers using state-of-the-art techniques in an innovative, collaborative environment that has led to several groundbreaking discoveries over the last three decades. Our focus is to investigate the mechanisms of action of the proteoglycans mentioned above in regulating the tumor microenvironment by altering catabolism, cell signaling, and angiogenesis, ultimately counteracting tumor growth (see figure below). The ideal candidates will have technical expertise in cell-based assays, qPCR, protein expression (e.g., ELISA, Western blot), cell migration/invasion assays, cancer mouse models, and confocal analysis. We are looking for candidates with acute attention to details, proficient reasoning skills in experimental design, execution, data analysis, statistical methods (GraphPad or SigmaPlot), and interpretation. Excellent written and verbal communication skills are also required. If you are interested, please submit your **C.V.** and three letters of reference to **Renato V. Iozzo** renato.iozzo@jefferson.edu



Autophagic induction of HAS2. *Representative super-resolution microscopy images of HUVEC treated with vehicle or Torin 1 (20 nM) for 4 h and immuno-labeled for ATG9A (green) and HAS2 (red). Nucleus (Nu) outlined in white dotted lines. Scale bar, 10 mm.*

1. Neill, T., Painter, H., Buraschi, S., Owens, R. T., Lisanti, M. P., Schaefer, L., and Iozzo, R. V. (2012) Decorin antagonizes the angiogenic network. Concurrent inhibition of Met, hypoxia inducible factor-1□□and vascular endothelial growth factor A and induction of thrombospondin-1 and TIMP3. *J. Biol. Chem.* **287,** 5492-5506
2. Buraschi, S., Pal, N., Tyler-Rubinstein, N., Owens, R. T., Neill, T., and Iozzo, R. V. (2010) Decorin antagonizes Met receptor activity and downregulates □-catenin and Myc levels. *J. Biol. Chem.* **285,** 42075-42085

3. Buraschi, S., Neill, T., Goyal, A., Poluzzi, C., Smythies, J., Owens, R. T., Schaefer, L., Torres, A., and Iozzo, R. V. (2013) Decorin causes autophagy in endothelial cells via Peg3. *Proc. Natl. Acad. Sci. U. S. A.* **110,** E2582-E2591
4. Neill, T., Andreuzzi, E., Wang, Z.-X., Peiper, S. C., Mongiat, M., and Iozzo, R. V. (2018) Endorepellin remodels the endothelial transcriptome toward a pro-autophagic and pro-mitophagic gene signature. *J. Biol. Chem.* **293,** 12137-12148
5. Chen, C. G., Gubbiotti, M. A., Kapoor, A., Han, X., Yu, Y., Linhardt, R. J., and Iozzo, R. V. (2020) Autophagic degradation of HAS2 in endothelial cells: A novel mechanism to regulate angiogenesis. *Matrix Biol* **90,** 1-19
6. Kapoor, A., Chen, C. G., and Iozzo, R. V. (2020) Endorepellin evokes an angiostatic stress signaling cascade in endothelial cells. *J. Biol Chem.* **295,** 6344-6356
7. Neill, T., Chen, C. G., Buraschi, S., and Iozzo, R. V. (2020) Catabolic degradation of endothelial VEGFA via autophagy. *J. Biol Chem.* **295,** 6064-6079

Postdoctoral Position Available To Study The Endocrinology of Bone

A position is available immediately in the laboratory of Dr. Gerard Karsenty at the Vagelos College of Physicians and Surgeons, Columbia University in New York City.

The goal of the laboratory is to demonstrate through state-of-the-art genetic, molecular and physiological approaches that many pathways regulating the most classical physiological functions in mammals remain to be discovered. A further goal of the laboratory is to show that harnessing these novel regulatory pathways may help treating degenerative diseases caused by the disruption of a given physiological process.

Our studies use bone as a model organ and focus largely on osteocalcin, a hormone regulating an unusually large number of physiological processes.

Current projects in the laboratory include but are not limited to:

- The description of novel functions of osteocalcin with a special emphasis on novel osteocalcin functions in the brain.
- The elucidation of it signaling pathway in various organs including the brain and the autonomic nervous system
- The of the influence of the maternal hormonal status and in particular maternal osteocalcin on physiology in the offspring.
- The extension of this work to the treatment of degenerative diseases.
- The exploration of novel pathways underlying metastases to bone of various cancers.

To carry out these and other projects, we are looking for MD, PhD or MD-PhDs skilled in molecular and cellular biology methods, biochemistry and cell culture and who are eager to discover new biology's. An experience in mouse genetics and neuroscience would be a plus.

For more information please contact Dr. Gerard Karsenty at gk2172@cumc.columbia.edu

Your application file should contain a complete CV, contact information or reference letter of 3 referees.

Columbia University seeks to nurture a work environment regardless of gender, age, cultural background or nationality. If you have any questions relating to accessibility or support, please contact us at cumchr@columbia.edu

Postdoctoral Researcher position

Project: "Mechanistic insights into the specificity of glycosaminoglycan interactions with regulatory proteins" at GAG Computational Group (www.comp-gag.org) at Faculty of Chemistry, University of Gdańsk, Poland.

The goal: is to understand molecular basis of the specificity in protein-glycosaminoglycan interactions by means of molecular modeling approaches, some of which will be developed in this study. The work will be carried out within intensive collaborations with NMR experiments performed on same molecular systems at the University of Leipzig. The result of this research will serve to guide the design of new methods for tissue regeneration and healing.

Requirements: PhD in Physics/Chemistry/Biology/Computer Sciences; solid experience with modeling techniques as molecular docking, molecular dynamics of biomolecular systems; experience with protein-carbohydrate systems is an advantage; solid experience with Linux environment; experience with scripting (python, bash, awk, R); interest in the interdisciplinary aspect of the project; proficiency in written and spoken English; excellent presenting and communication skills.

Research tasks: molecular docking of glycosaminoglycans and their mimetics; molecular dynamics-based analysis of protein-glycosaminoglycan, protein-small molecules, protein-DNA/RNA systems; participation in writing publications and presentation of the results at scientific meetings.

Financial source: BEETHOVEN CLASSIC Grant from the The National Science Centre of Poland.

Terms of employment: full time employment up to 18 months, salary: 120 000 PLN/year (brutto brutto).
Application deadline: until the position is filled.
Starting date: flexible.
Collaborations within the project: University of Leipzig (Research Group of prof. Daniel Huster).
How to apply: send your CV to dr hab. Sergey Samsonov via e-mail sergey.samsonov@ug.edu.pl

Research Assistant position

Applications are invited for a Research Assistant position funded by the British Heart Foundation, in the Department of Immunology and Inflammation at Imperial College London. You will join a team based in Dr Josefin Ahnström's laboratory at Imperial College under the supervision of Dr. Salvatore Santamaria. The purpose of this project is determining the molecular mechanisms behind the development of Thoracic aortic aneurysms and dissections (TAAD) by characterising cleavage of aortic proteoglycans by ADAMTS proteases. Proteoglycans from different sources (recombinantly-expressed, extracted from mouse tissues and human patients) will be purified and subjected to mass spectrometry analysis to analyse their cleavage. You will support Dr. Salvatore Santamaria with expression and purification of recombinant proteoglycans and ADAMTS proteases as well as proteoglycan extraction from human and mouse tissues. You will also use a range of experimental techniques including ELISA, FPLC, FRET assays, western blot and SDS-PAGE alongside proteomics.

You will take on a supporting role in achieving the aims of the project. You are also expected to take part in academic activities, including contributing to lab meetings and presentations.

Essential requirements

A good first degree or equivalent (MSc / BSc) in Biological Science or related discipline
Experience of cell culture, protein expression and purification.
Able to conduct a detailed review of recent literature and develop and apply new concepts.

Contact Salvatore Santamaria: s.santamaria@imperial.ac.uk
Reference MED02208 This is a full time, fixed term post until 22 October 2023
Closing date 11 February 2021
https://www.imperial.ac.uk/jobs/description/MED02208/research-assistant

Spotlights on methods that other ISMB members may find useful

If you would like to feature in the next newsletter, please email Communication Group Coordinator Julia Etich (Julia.Etich@kgu.de)

TAIL TENDON BREAK TIME FOR THE ASSESSMENT OF AGING AND LONGITUDINAL HEALTHSPAN IN MICE

Haefke As, Ewald CY
Corresponding author: collin-ewald@ethz.ch
Bio-101: e3833, DOI:10.21769/BioProtoc.3833, https://bio-protocol.org/e3833

Abstract: The successful evaluation of longevity-promoting interventions requires the identification of reliable biomarkers of healthspan and lifespan. Non-enzymatic glycation end-products accumulate on collagens during the aging process, leading to the crosslinking and stiffening of collagen fibers. In murine species, the glycation of collagen during aging can be indirectly quantified by the Tail Tendon Break Time (TTBT) assay. Importantly, longitudinal linear increases in TTBTs across age are decreased by multiple established longevity-promoting

interventions. Here, we discuss experimental considerations for the TTBT assay and provide an adapted version of the original TTBT protocol from Harrison and Archer 1978. We propose that TTBT remains a useful and minimally-invasive readout of longevity, especially when considered in combination with other longitudinal healthspan assaying protocols.

A FIJI MACRO FOR QUANTIFYING PATTERN IN EXTRACELLULAR MATRIX

Wershof E, Park D, Barry DJ, Jenkins RP, Rullan A, Wilkins A, Roxanis I, Anderson KI, Bates PA*, Sahai E*
***Corresponding authors**: erik.sahai@crick.ac.uk
bioRix preprint, doi : https://doi.org/10.1101/86750, July 11, 2020

Abstract: Diverse extracellular matrix patterns are observed in both normal and pathological tissue. However, most current tools for quantitative analysis focus on a single aspect of matrix patterning. Thus, an automated pipeline that simultaneously quantifies a broad range of metrics and enables a comprehensive description of varied matrix patterns is needed. To this end we have developed **an ImageJ plugin** called **TWOMBLI**, which stands for **The Workflow Of Matrix BioLogy Informatics**. TWOMBLI is designed to be quick, versatile and easy-to-use particularly for non-computational scientists. TWOMBLI can be downloaded from https://github.com/wershofe/TWOMBLI together with detailed documentation. Here we present an overview of the pipeline together with examples from a wide range of contexts where matrix patterns are generated

A NOVEL RGB-TRICHROME STAINING METHOD FOR ROUTINE HISTOLOGICAL ANALYSIS OF MUSCULOSKELETAL TISSUES

Gaytan F, Morales C, Reymundo C, Tena-Sempere M. Sci Rep. 2020 Oct 7;10(1):16659. doi: 10.1038/s41598-020-74031-x.
Corresponding author: bc1galuf@uco.es

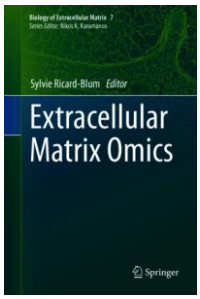
Abstract: Morphometry and histology are essential approaches for investigation and diagnosis of musculo-skeletal disorders. Despite the advent of revolutionary methods of image analysis and high resolution three-dimensional imaging technology, basic conventional light microscopy still provides an incisive overview of the structure and tissue dynamics of the musculoskeletal system. This is crucial to both preclinical and clinical research, since several clinically relevant processes, such as bone repair, osteoarthritis, and metabolic bone diseases, display distinct, if not pathognomonic, histological features. Due to the particular characteristics of the skeletal tissues (i.e., the existence of mineralized extracellular matrices), a large number of staining methods applicable to either decalcified or undecalcified tissues are available. However, it is usually the case that several staining methods need to be sequentially applied in order to achieve the different endpoints required to fully assess skeletal tissue structure and dynamics, and to allow morphometric quantification. We describe herein a novel staining method, the RGB trichrome, amenable for application to decalcified, paraffin embedded human musculoskeletal tissues. The acronym RGB corresponds to the three primary dyes used: picrosirius Red, fast Green, and alcian Blue. Although these individual pigments are commonly used either isolated, in binary combinations, or as part of more complex polychrome staining methods, when merged in the RGB trichrome staining produce high-quality/high-contrast images, permitting not only clear identification of different tissues (i.e., the different types of cartilage, bone and fibrous connective tissue), but also discrimination between calcified and uncalcified bone and cartilage, as well as an unexpected diversity of shades of color, while displaying singular properties among polychrome staining

methods, such as the unveiling of the bone osteocyte dendritic/canalicular network. Hence, we propose the RGB trichrome as simple but highly-reliable tool for the preclinical and clinical study of the musculoskeletal system.

BOOKS & SPECIAL ISSUES ON THE EXTRACELLULAR MATRIX

Extracellular Matrix Omics, Sylvie Ricard-Blum editor
Series: Biology of Extracellular Matrix
Series Editor: Nikos K. Karamanos
Edited by Springer

https://link.springer.com/book/10.1007%2F978-3-030-58330-9



The Extracellular Matrix Goes -Omics: Resources and Tools
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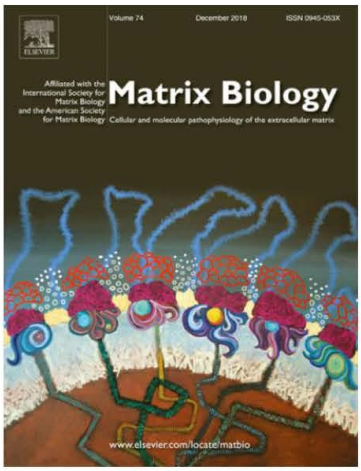
Beyond the Matrisome:
New Frontiers in ECM Research
A Special Issue of *Matrix Biology*
Edited by Alexandra Naba and Suneel Apte



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

Research articles submitted for consideration for the Special Issue can span the full bandwidth of -omic applications for mechanistic ECM research, new developments in understanding molecular networks within the ECM, or mechanistic studies on ECM molecules and complexes, covering the breadth of the field from fundamental molecular sciences to applications to development, diseases, and tissue engineering.

On behalf of Renato Iozzo, Editor-in-Chief of *Matrix Biology*, we invite you to contribute a research article for this upcoming Special Issue of *Matrix Biology*, which offers the quality, visibility and impact (2019 IF: 8.572) that you would expect from the flagship journal in ECM research, combined with the convenience and reach of open access. Articles will be published online, quickly after acceptance, and constantly so there are no print delays or long waits for publication**. The deadline for manuscript submission for consideration for the Special Issue is August 31, 2021.**

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- Please make sure to select the name of the Special Issue when uploading your manuscript. Please also mention the name of the Special Issue in your cover letter as well.
- Include the names and emails of four potential expert reviewers. All the manuscripts will be peer-reviewed.
- Please follow *Matrix Biology*'s authors guidelines to prepare your manuscript.
- Include the mandatory Highlights, in bullet form with 87 characters maximum.
- When appropriate, please try to cite papers published in *Matrix Biology* or in *Matrix Biology Plus* in the past three years.

We look forward to receiving your contribution to this Special Issue of *Matrix Biology*.

Best wishes.

Alexandra Naba, PhD
University of Illinois-Chicago

Suneel S. Apte, MBBS, DPhil
Cleveland Clinic Lerner Research Institute

RECENT PAPERS

The extracellular matrix phenome across species
Matrix Biology Plus 2020, https://doi.org/10.1016/j.mbplus.2020.100039
Statzer C, Ewald CY.
Corresponding author: collin-ewald@ethz.ch
Abstract: *Extracellular matrices are essential for cellular and organismal function. Recent genome-wide and phenome-wide association studies started to reveal a broad spectrum of phenotypes associated with genetic variants. However, the phenome or spectrum of all phenotypes associated with genetic variants in extracellular matrix genes is unknown. Here, we analyzed over two million recorded genotype-to-phenotype relationships across multiple species to define their extracellular matrix phenomes. By using the previously defined matrisomes of humans, mice, zebrafish, Drosophila, and C. elegans, we found that the extracellular matrix phenome comprises of 3–10% of the entire phenome. Collagens (COL1A1, COL2A1) and fibrillin (FBN1) are each associated with >150 distinct phenotypes in humans, whereas collagen COL4A1, Wnt- and sonic hedgehog (shh) signaling are predominantly associated in other species. We determined the phenotypic fingerprints of matrisome genes and found that MSTN, CTSD, LAMB2, HSPG2, and COL11A2 and their corresponding orthologues have the most phenotypes across species. Out of the 42,551 unique matrisome genotype-to-phenotype relationships across the five species with defined matrisomes, we have constructed interaction networks to identify the underlying molecular components connecting with orthologues phenotypes and with novel phenotypes. Thus, our networks provide a framework to predict unassessed phenotypes and their potential underlying molecular interactions. These frameworks inform on matrisome genotype-to-phenotype relationships and potentially provide a sophisticated choice of biological model system to study human phenotypes and diseases.*

Activin-mediated alterations of the fibroblast transcriptome and matrisome control the biomechanical properties of skin wounds.
Wietecha MS, Pensalfini M, Cangkrama M, Müller B, Jin J, Brinckmann J, Mazza E, Werner S. Nat Commun. 2020 11:2604. doi: 10.1038/s41467-020-16409-z.
Corresponding author: sabine.werner@biol.ethz.ch
Abstract: *Matrix deposition is essential for wound repair, but when excessive, leads to hypertrophic scars and fibrosis. The factors that control matrix deposition in skin wounds have only partially been identified and the consequences of matrix alterations for the mechanical properties of wounds are largely unknown. Here, we report how a single diffusible factor, activin A, affects the healing process across scales. Bioinformatics analysis of wound fibroblast transcriptome data combined with biochemical and histopathological analyses of wounds and functional in vitro studies identify that activin promotes pro-fibrotic gene expression signatures and processes, including glycoprotein and proteoglycan biosynthesis, collagen deposition, and altered collagen cross-linking. As a consequence, activin strongly reduces the wound and scar deformability, as identified by a non-invasive in vivo method for biomechanical analysis. These results provide mechanistic insight into the roles of activin in wound repair and fibrosis and identify the functional consequences of alterations in the wound matrisome at the biomechanical level.*

Exosomes for Wound Healing: Purification Optimization and Identification of Bioactive Components.
Hettich BF, Ben-Yehuda Greenwald M, Werner S, Leroux JC. Adv Sci (Weinh). 2020 7:2002596. doi: 10.1002/advs.202002596.

Corresponding author: jleroux@ethz.ch
Abstract: *Human mesenchymal stem cell exosomes have been shown to promote cutaneous wound healing. Their bioactivity is most often attributed to their protein and nucleic acid components, while the function of exosomal lipids remains comparatively unexplored. This work specifically assesses the involvement of lipids and the transmembrane enzyme CD73 in the exosomes' biological activity in stimulating the cutaneous wound healing process. Since exosome preparation processes are not harmonized yet, certain production and purification parameters are first systematically investigated, enabling the optimization of a standardized protocol delivering high exosome integrity, yield, and purity. An in situ enzymatic assay is introduced to specifically assess the vesicle functionality, and quantitative proteomics is employed to establish the cell culture conditions yielding a stable exosome protein profile. Using a combination of in vitro approaches, CD73 and constitutional lipids of HPV-16 E6/E7 transformed human bone marrow stromal cell-derived exosomes are identified as key bioactive components promoting the exosome-driven acceleration of processes required for wound repair. A pilot wound healing study in mice indeed suggests a role of lipids in the exosomes' biological activity. Strikingly, the extent of the bioactivity of these exosomal components is found to be dependent on the target cell type.*

The Interactome of Cancer-Related Lysyl Oxidase and Lysyl Oxidase-Like Proteins

Vallet SD, Berthollier C, Salza R, Muller L, Ricard-Blum S. Cancers (Basel) 2020 Dec 29;13(1):E71. doi: 10.3390/cancers13010071
Corresponding author: sylvie.ricard-blum@univ-lyon1.fr
Abstract: *The members of the lysyl oxidase (LOX) family are amine oxidases, which initiate the covalent cross-linking of the extracellular matrix (ECM), regulate ECM stiffness, and contribute to cancer progression. The aim of this study was to build the first draft of the interactome of the five members of the LOX family in order to determine its molecular functions, the biological and signaling pathways mediating these functions, the biological processes it is involved in, and if and how it is rewired in cancer. In vitro binding assays, based on surface plasmon resonance and bio-layer interferometry, combined with queries of interaction databases and interaction datasets, were used to retrieve interaction data. The interactome was then analyzed using computational tools. We identified 31 new interactions and 14 new partners of LOXL2, including the α5β1 integrin, and built an interactome comprising 320 proteins, 5 glycosaminoglycans, and 399 interactions. This network participates in ECM organization, degradation and cross-linking, cell-ECM interactions mediated by non-integrin and integrin receptors, protein folding and chaperone activity, organ and blood vessel development, cellular response to stress, and signal transduction. We showed that this network is rewired in colorectal carcinoma, leading to a switch from ECM organization to protein folding and chaperone activity*.

GAG-DB, the New Interface of the Three-Dimensional Landscape of Glycosaminoglycans.

Pérez S, Bonnardel F, Lisacek F, Imberty A, Ricard Blum S, Makshakova O. Biomolecules. 2020 10(12):1660.
Corresponding author: spsergeperez@gmail.com
Abstract: *Glycosaminoglycans (GAGs) are complex linear polysaccharides. GAG-DB is a curated database that classifies the three-dimensional features of the six mammalian GAGs (chondroitin sulfate, dermatan sulfate, heparin, heparan sulfate, hyaluronan, and keratan sulfate) and their oligosaccharides complexed with proteins. The entries are structures of GAG and GAG-protein complexes determined by X-ray single-crystal diffraction methods, X-ray fiber diffractometry, solution NMR spectroscopy, and scattering data often associated with molecular modeling. We designed the database architecture and the navigation tools to query the database with the Protein Data Bank (PDB), UniProtKB, and GlyTouCan (universal glycan repository) identifiers. Special attention was devoted to the description of the bound glycan ligands using simple graphical representation and numerical format for cross-referencing to other databases in glycoscience and functional data. GAG-DB provides detailed information on GAGs, their bound protein ligands, and features their interactions using several open access applications. Binding covers*

interactions between monosaccharides and protein monosaccharide units and the evaluation of quaternary structure. GAG-DB is freely available.

Role of oligosaccharide chain polarity in protein-glycosaminoglycan interactions.
Bojarski K.K., Samosnov S.A. J Chem Inf Mod. 2020 Dec 30. doi: 10.1021/acs.jcim.0c01402. Online ahead of print.
Corresponding author: sergey.samsonov@ug.edu.pl
Abstract: *Glycosaminoglycans (GAGs) are long unbranched anionic polysaccharides made up of repetitive disaccharide units involved in biologically relevant processes in the extracellular matrix such as cell proliferation and communication. A GAG can be bound in antiparallel energetically comparable orientations on the protein surface, and these orientations are, therefore, difficult to distinguish both experimentally and computationally. In this study, for the first time we analyzed the impact of the GAG chain polarity on the interactions with Fibroblast Growth Factors-1 and -2 (FGF-1 and FGF-2). We performed a series of 1 μs molecular dynamics simulations of the FGF-1 and FGF-2 complexes with heparin (HP), a GAG representative, of different length. We analyzed the relationship between the HP orientation, energetic, and conformational space characteristics of FGF-1-HP and FGF-2-HP complexes. We concluded that HP can be bound by these proteins in the same binding sites but in different orientations, while the orientation present in the experimental structure might be favorable. Our data presented in this study provide a novel view on the impact of GAG polarity on the specificity of protein-GAG complex formation, which is an essential aspect for the proper understanding of the intermolecular interactions in these systems.*

Computational insights into the calcium ions role in protein-glycosaminoglycan systems.
Kogut M.M., Maszota-Zieleniak M., Marcisz M., Samsonov S.A. Phys. Chem. Chem. Phys., 2021, Accepted Manuscript. https://doi.org/10.1039/D0CP05438K
Corresponding author: sergey.samsonov@ug.edu.pl
Abstract: *Glycosaminoglycans (GAGs) are anionic periodic, linear polysaccharides which are composed of periodic disaccharide units. They play a vital role in many biological processes ongoing in the extracellular matrix. In terms of computational approaches, GAGs are very challenging molecules due to their high flexibility, periodicity, predominantly electrostatics-driven nature of interactions with their protein counterparts and potential multipose binding. Furthermore, the molecular mechanisms underlying GAG-mediated interactions are not fully known yet, and experimental techniques alone are not always sufficient to gain insights into them. The aim of this study was to characterize protein-ion-GAG complexes for the systems where ions are directly involved in GAG binding. Molecular docking, molecular dynamics and free energy calculations approaches were applied to model and rigorously analyse interactions between annexins (II and V), calcium ions (Ca2+) and heparin (HP). The computational data were examined and discussed in the context of the structural data previously reported by crystallographic studies. The computational results confirm that the presence of Ca2+ has a tremendous impact on the annexin-HP binding site. This study provides a general computational pipeline to discover the complexity of protein-GAG interactions and helps to understand the role of ions involved at the atomic level. The limitations of the applied protocols are described and discussed pointing at the challenges persisting in state-of-art in silico tools to study protein-ion-GAG systems.*

Exosite inhibition of ADAMTS-5 by a glycoconjugated arylsulfonamide
Santamaria S, Cuffaro D, Nuti E, Ciccone L, Tuccinardi T, Liva F, D'AndreaF, de Groot R, Rossello A, Ahnström J. Scientific Reports volume 11, Article number: 949 (2021). doi.org/10.1038/s41598-020-80294-1
Corresponding author: s.santamaria@imperial.ac.uk and elisa.nuti@unipi.it
Abstract: *ADAMTS-5 is a major protease involved in the turnover of proteoglycans such as aggrecan and versican. Dysregulated aggrecanase activity of ADAMTS-5 has been directly linked to the etiology of osteoarthritis (OA). For this reason, ADAMTS-5 is a pharmaceutical target for the treatment of OA. ADAMTS-5 shares high structural and*

functional similarities with ADAMTS-4, which makes the design of selective inhibitors particularly challenging. Here we exploited the ADAMTS-5 binding capacity of β-N-acetyl-d-glucosamine to design a new class of sugar-based arylsulfonamides. Our most promising compound, 4b, is a non-zinc binding ADAMTS-5 inhibitor which showed high selectivity over ADAMTS-4. Docking calculations combined with molecular dynamics simulations demonstrated that 4b is a cross-domain inhibitor that targets the interface of the metalloproteinase and disintegrin-like domains. Furthermore, the interaction between 4b and the ADAMTS-5 Dis domain is mediated by hydrogen bonds between the sugar moiety and two lysine residues (K532 and K533). Targeted mutagenesis of these two residues confirmed their importance both for versicanase activity and inhibitor binding. This positively-charged cluster of ADAMTS-5 represents a previously unknown substrate-binding site (exosite) which is critical for substrate recognition and can therefore be targeted for the development of selective ADAMTS-5 inhibitors

ADAMTS proteases in cardiovascular physiology and disease.
Santamaria S, de Groot R. Open Biol. 2020 Dec;10(12):200333. doi: 10.1098/rsob.200333.
Corresponding author: s.santamaria@imperial.ac.uk and r.degroot@ucl.ac.uk
Abstract: *The a disintegrin-like and metalloproteinase with thrombospondin motif (ADAMTS) family comprises 19 proteases that regulate the structure and function of extracellular proteins in the extracellular matrix and blood. The best characterized cardiovascular role is that of ADAMTS-13 in blood. Moderately low ADAMTS-13 levels increase the risk of ischeamic stroke and very low levels (less than 10%) can cause thrombotic thrombocytopenic purpura (TTP). Recombinant ADAMTS-13 is currently in clinical trials for treatment of TTP. Recently, new cardiovascular roles for ADAMTS proteases have been discovered. Several ADAMTS family members are important in the development of blood vessels and the heart, especially the valves. A number of studies have also investigated the potential role of ADAMTS-1, -4 and -5 in cardiovascular disease. They cleave proteoglycans such as versican, which represent major structural components of the arteries. ADAMTS-7 and -8 are attracting considerable interest owing to their implication in atherosclerosis and pulmonary arterial hypertension, respectively. Mutations in the ADAMTS19 gene cause progressive heart valve disease and missense variants in ADAMTS6 are associated with cardiac conduction. In this review, we discuss in detail the evidence for these and other cardiovascular roles of ADAMTS family members, their proteolytic substrates and the potential molecular mechanisms involved.*

Diversity of Mechanisms Underlying Latent TGF-β Activation in Recessive Dystrophic Epidermolysis Bullosa.
Akasaka E, Kleiser S, Sengle G, Bruckner-Tuderman L, Nyström A. J Invest Dermatol. 2020 Dec 14:S0022-202X(20)32357-5. doi: 10.1016/j.jid.2020.10.024.
Corresponding author: alexander.nystroem@uniklinik-freiburg.de
Abstract: *Injury- and inflammation-driven progressive dermal fibrosis is a severe manifestation of recessive dystrophic epidermolysis bullosa (RDEB) - a genetic skin blistering disease caused by mutations in COL7A1. Transforming growth factor-β1 (TGF-β) activation plays a prominent part in progressing dermal fibrosis. However, the underlying mechanisms are not fully elucidated. TGF-β is secreted in a latent form, which has to be activated for its biological functions. In this study, we determined that RDEB fibroblasts have an enhanced capacity to activate the latent form. Mechanistic and functional assessment demonstrated that this process depends on multiple latent TGF-β activators, including thrombospondin-1, RGD-binding integrins, matrix metalloproteinases and reactive oxygen species, which act in concert, in a self-perpetuating feedback loop to progress fibrosis. Importantly, our study also disclosed keratinocytes as prominent facilitators of fibrosis in RDEB. They stimulate microenvironmental latent TGF-β activation via enhanced production of the above mediators. Collectively, our study provides data on the molecular mechanism behind dysregulated TGF-β signaling in RDEB, which are much needed for development of evidence-based fibrosis-delaying treatments.*

miR-127-3p is an epigenetic activator of myofibroblast senescence situated within the miRNA enriched Dlk1-Dio3 imprinted domain on mouse chromosome 12.
Auler M, Bergmeier V, Georgieva VS, Pitzler L, Frie C, Nüchel J, Eckes B, Hinz B, Brachvogel B. J Invest Dermatol. 2020 Dec 3:S0022-202X(20)32356-3. doi: 10.1016/j.jid.2020.11.011.
Corresponding author: bent.brachvogel@uni-koeln.de
Abstract: *During wound healing, fibroblasts differentiate into non-proliferative contractile myofibroblasts, contribute to skin repair, and eventually undergo apoptosis or become senescent. MicroRNAs (miR) are posttranscriptional regulators of gene expression networks that control cell fate and survival and may also regulate senescence. Here we determined regulated miRs in myofibroblasts isolated from wounds and analyzed their role in senescent myofibroblast formation. Transcriptome profiling showed that a 200 kbp region of the Dlk1-Dio3 imprinted domain on mouse chromosome 12 encodes for most of the upregulated miRs in the entire genome of mouse myofibroblasts. Among those, miR-127-3p induced a myofibroblast-like phenotype associated with a block in proliferation. Molecular analysis revealed that miR-127-3p induced a prolonged cell-cycle arrest with unique molecular features of senescence, including the activation of the senescence-associated ß-galactosidase, increase in p53 and p21 levels, inhibition of lamin B1, proliferation factors, and the production of senescence-associated inflammatory and extracellular matrix-remodeling components. Hence, miR-127-3p emerges as an epigenetic activator regulating the transition from repair to remodeling during skin wound healing, but may also induce age-related defects, pathological scarring and fibrosis, all linked to myofibroblast senescence.*

A Set of Cell Lines Derived from a Genetic Murine Glioblastoma Model Recapitulates Molecular and Morphological Characteristics of Human Tumors.
Costa B, Fletcher MNC, Boskovic P, Ivanova EL, Eisemann T, Lohr S, Bunse L, Löwer M, Burchard S, Korshunov A, Coltella N, Cusimano M, Naldini L, Liu HK, Platten M, Radlwimmer B, Angel P, Peterziel H. Cancers (Basel). 2021 Jan 10;13(2):E230. doi: 10.3390/cancers13020230.
Corresponding author: b.costa@dkfz.de and p.angel@dkfz.de
Abstract: *Glioblastomas (GBM) are the most aggressive tumors affecting the central nervous system in adults, causing death within, on average, 15 months after diagnosis. Immunocompetent in-vivo models that closely mirror human GBM are urgently needed for deciphering glioma biology and for the development of effective treatment options. The murine GBM cell lines currently available for engraftment in immunocompetent mice are not only exiguous but also inadequate in representing prominent characteristics of human GBM such as infiltrative behavior, necrotic areas, and pronounced tumor heterogeneity. Therefore, we generated a set of glioblastoma cell lines by repeated in vivo passaging of cells isolated from a neural stem cell-specific Pten/p53 double-knockout genetic mouse brain tumor model. Transcriptome and genome analyses of the cell lines revealed molecular heterogeneity comparable to that observed in human glioblastoma. Upon orthotopic transplantation into syngeneic hosts, they formed high-grade gliomas that faithfully recapitulated the histopathological features, invasiveness and immune cell infiltration characteristic of human glioblastoma. These features make our cell lines unique and useful tools to study multiple aspects of glioblastoma pathomechanism and to test novel treatments in an intact immune microenvironment.*

Short-term Response of Serum Cartilage Oligomeric Matrix Protein to Different Types of Impact Loading Under Normal and Artificial Gravity.
Dreiner M, Willwacher S, Kramer A, Kümmel J, Frett T, Zaucke F, Liphardt AM, Gruber M, Niehoff A. Front Physiol. 2020 Aug 31;11:1032. doi: 10.3389/fphys.2020.01032.
Corresponding author: niehoff@dshs-koeln.de
Abstract: *Microgravity during long-term space flights induces degeneration of articular cartilage. Artificial gravity through centrifugation combined with exercise has been suggested as a potential countermeasure for*

musculoskeletal degeneration. The purpose of this study was to investigate the effect of different types of impact loading under normal and artificial gravity conditions on serum concentrations of cartilage oligomeric matrix protein (COMP), a biomarker of cartilage metabolism. Fifteen healthy male adults (26 ± 4 years, 181 ± 4 cm, 77 ± 6 kg) performed four different 30-min impact loading protocols on four experimental days: jumping with artificial gravity elicited by centrifugation in a short-arm centrifuge (AGJ), jumping with artificial gravity generated by low-pressure cylinders in a sledge jump system (SJS), vertical jumping under Earth gravity (EGJ), and running under Earth gravity (RUN). Five blood samples per protocol were taken: 30 min before, immediately before, immediately after, 30 min after, and 60 min after impact loading. Serum COMP concentrations were analyzed in these samples. During the impact exercises, ground reaction forces were recorded. Peak ground reaction forces were significantly different between the three jumping protocols ($p < 0.001$), increasing from AGJ (14 N/kg) to SJS (22 N/kg) to EGJ (29 N/kg) but were similar in RUN (22 N/kg) compared to SJS. The serum COMP concentration was increased ($p < 0.001$) immediately after all loading protocols, and then decreased ($p < 0.001$) at 30 min post-exercise compared to immediately after the exercise. Jumping and running under Earth gravity (EGJ and RUN) resulted in a significantly higher ($p < 0.05$) increase of serum COMP levels 30 min after impact loading compared to the impact loading under artificial gravity (RUN +30%, EGJ +20%, AGJ +17%, and SJS +13% compared to baseline). In conclusion, both the amplitude and the number of the impacts contribute to inducing higher COMP responses and are therefore likely important factors affecting cartilage metabolism. RUN had the largest effect on serum COMP concentration, presumably due to the high number of impacts, which was 10 times higher than for the jump modalities. Future studies should aim at establishing a dose-response relationship for different types of exercise using comparable amounts of impacts.

Extracellular matrix plasticity as a driver of cell spreading.

Grolman JM, Weinand P, Mooney DJ. Proc Natl Acad Sci U S A. 2020 Oct 20;117(42):25999-26007. doi: 10.1073/pnas.2008801117.

Corresponding author: mooneyd@seas.harvard.edu

Abstract: *Mammalian cell morphology has been linked to the viscoelastic properties of the adhesion substrate, which is particularly relevant in biological processes such as wound repair and embryonic development where cell spreading and migration are critical. Plastic deformation, degradation, and relaxation of stress are typically coupled in biomaterial systems used to explore these effects, making it unclear which variable drives cell behavior. Here we present a nondegradable polymer architecture that specifically decouples irreversible creep from stress relaxation and modulus. We demonstrate that network plasticity independently controls mesenchymal stem cell spreading through a biphasic relationship dependent on cell-intrinsic forces, and this relationship can be shifted by inhibiting actomyosin contractility. Kinetic Monte Carlo simulations also show strong correlation with experimental cell spreading data as a function of the extracellular matrix (ECM) plasticity. Furthermore, plasticity regulates many ECM adhesion and remodeling genes. Altogether, these findings confirm a key role for matrix plasticity in stem cell biophysics, and we anticipate this will have ramifications in the design of biomaterials to enhance therapeutic applications of stem cells.*

β1 Integrin regulates convergent extension in mouse notogenesis, ensures notochord integrity and the morphogenesis of vertebrae and intervertebral discs.

Guo SS, Au TYK, Wynn S, Aszodi A, Chan D, Fässler R, Cheah KSE. Development. 2020 Nov 18;147(22):dev192724. doi: 10.1242/dev.192724.

Corresponding author: kathycheah@hku.hk

Abstract: *Background: The notochord drives longitudinal growth of the body axis by convergent extension, a highly conserved developmental process that depends on non-canonical Wnt/planar cell polarity (PCP) signaling. However, the role of cell-matrix interactions mediated by integrins in the development of the notochord is unclear. We*

developed transgenic Cre mice, in which the β1 integrin gene (Itgb1) is ablated at E8.0 in the notochord only or in the notochord and tail bud. These Itgb1 conditional mutants display misaligned, malformed vertebral bodies, hemi-vertebrae and truncated tails. From early somite stages, the notochord was interrupted and displaced in these mutants. Convergent extension of the notochord was impaired with defective cell movement. Treatment of E7.25 wild-type embryos with anti-β1 integrin blocking antibodies, to target node pit cells, disrupted asymmetric localization of VANGL2. Our study implicates pivotal roles of β1 integrin for the establishment of PCP and convergent extension of the developing notochord, its structural integrity and positioning, thereby ensuring development of the nucleus pulposus and the proper alignment of vertebral bodies and intervertebral discs. Failure of this control may contribute to human congenital spine malformations.

EMILIN proteins are novel extracellular constituents of the dentin-pulp complex.
Imhof T, Korkmaz Y, Koch M, Sengle G, Schiavinato A. Sci Rep. 2020 Sep 18;10(1):15320. doi: 10.1038/s41598-020-72123-2.
Corresponding author: gsengle@uni-koeln.de and aschiav1@uni-koeln.de
Abstract: *Odontoblasts and pulp stroma cells are embedded within supramolecular networks of extracellular matrix (ECM). Fibrillin microfibrils and associated proteins are crucial constituents of these networks, serving as contextual scaffolds to regulate tissue development and homeostasis by providing both structural and mechanical properties and sequestering growth factors of the TGF-β superfamily. EMILIN-1, -2, and -3 are microfibril-associated glycoproteins known to modulate cell behaviour, growth factor activity, and ECM assembly. So far their expression in the various cells of the dentin-pulp complex during development, in the adult stage, and during inflammation has not been investigated. Confocal immunofluorescence microscopy and western blot analysis of developing and adult mouse molars and incisors revealed an abundant presence of EMILINs in the entire dental papilla, at early developmental stages. Later in development the signal intensity for EMILIN-3 decreases, while EMILIN-1 and -2 staining appears to increase in the pre-dentin and in the ECM surrounding odontoblasts. Our data also demonstrate new specific interactions of EMILINs with fibulins in the dentin enamel junction. Interestingly, in dentin caries lesions the signal for EMILIN-3 was significantly increased in inflamed odontoblasts. Overall our findings point for the first time to a role of EMILINs in dentinogenesis, pulp biology, and inflammation.*

Epithelial loss of mitochondrial oxidative phosphorylation leads to disturbed enamel and impaired dentin matrix formation in postnatal developed mouse incisor.
Imhof T, Rosenblatt K, Pryymachuk G, Weiland D, Noetzel N, Deschner J, Baris OR, Kimoloi S, Koch M, Wiesner RJ, Korkmaz Y. Sci Rep. 2020 Dec 16;10(1):22037. doi: 10.1038/s41598-020-77954-7.
Corresponding author: rudolf.wiesner@uni-koeln.de and yueksel.korkmaz@unimedizin-mainz.de
Abstract: *The formation of dentin and enamel matrix depends on reciprocal interactions between epithelial-mesenchymal cells. To assess the role of mitochondrial function in amelogenesis and dentinogenesis, we studied postnatal incisor development in K320E-TwinkleEpi mice. In these mice, a loss of mitochondrial DNA (mtDNA), followed by a severe defect in the oxidative phosphorylation system is induced specifically in Keratin 14 (K14+) expressing epithelial cells. Histochemical staining showed severe reduction of cytochrome c oxidase activity only in K14+ epithelial cells. In mutant incisors, H&E staining showed severe defects in the ameloblasts, in the epithelial cells of the stratum intermedium and the papillary cell layer, but also a disturbed odontoblast layer. The lack of amelogenin in the enamel matrix of K320E-TwinkleEpi mice indicated that defective ameloblasts are not able to form extracellular enamel matrix proteins. In comparison to control incisors, von Kossa staining showed enamel biomineralization defects and dentin matrix impairment. In mutant incisor, TUNEL staining and ultrastructural analyses revealed differentiation defects, while in hair follicle cells apoptosis is prevalent. We concluded that mitochondrial oxidative phosphorylation in epithelial cells of the developed incisor is required for Ca2+ homeostasis*

to regulate the formation of enamel matrix and induce the differentiation of ectomesenchymal cells into odontoblasts.

Collagen XII mediated cellular and extracellular mechanisms regulate establishment of tendon structure and function.

Izu Y, Adams SM, Connizzo BK, Beason DP, Soslowsky LJ, Koch M, Birk DE. Matrix Biol. 2020 Oct 20:S0945-053X(20)30094-9. doi: 10.1016/j.matbio.2020.10.004.

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Abstract: *Tendons have a uniaxially aligned structure with a hierarchical organization of collagen fibrils crucial for tendon function. Collagen XII is expressed in tendons and has been implicated in the regulation of fibrillogenesis. It is a non-fibrillar collagen belonging to the Fibril-Associated Collagens with Interrupted Triple Helices (FACIT) family. Mutations in COL12A1 cause myopathic Ehlers Danlos Syndrome with a clinical phenotype involving both joints and tendons supporting critical role(s) for collagen XII in tendon development and function. Here we demonstrate the molecular function of collagen XII during tendon development using a Col12a1 null mouse model. Col12a1 deficiency altered tenocyte shape, formation of interacting cell processes, and organization resulting in impaired cell-cell communication and disruption of hierarchal structure as well as decreased tissue stiffness. Immuno-localization revealed that collagen XII accumulated on the tenocyte surface and connected adjacent tenocytes by building matrix bridges between the cells, suggesting that collagen XII regulates intercellular communication. In addition, there was a decrease in fibrillar collagen I in collagen XII deficient tenocyte cultures compared with controls suggesting collagen XII signaling specifically alters tenocyte biosynthesis. This suggests that collagen XII provides feedback to tenocytes regulating extracellular collagen I. Together, the data indicate dual roles for collagen XII in determination of tendon structure and function. Through association with fibrils it functions in fibril packing, fiber assembly and stability. In addition, collagen XII influences tenocyte organization required for assembly of higher order structure; intercellular communication necessary to coordinate long range order and feedback on tenocytes influencing collagen synthesis. Integration of both regulatory roles is required for the acquisition of hierarchal structure and mechanical properties.*

Glutamine Metabolism Controls Stem Cell Fate Reversibility and Long-Term Maintenance in the Hair Follicle.

Kim CS, Ding X, Allmeroth K, Biggs LC, Kolenc OI, L'Hoest N, Chacón-Martínez CA, Edlich-Muth C, Giavalisco P, Quinn KP, Denzel MS, Eming SA, Wickström SA. Cell Metab. 2020 Oct 6;32(4):629-642.e8. doi: 10.1016/j.cmet.2020.08.011.

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Abstract: *Stem cells reside in specialized niches that are critical for their function. Upon activation, hair follicle stem cells (HFSCs) exit their niche to generate the outer root sheath (ORS), but a subset of ORS progeny returns to the niche to resume an SC state. Mechanisms of this fate reversibility are unclear. We show that the ability of ORS cells to return to the SC state requires suppression of a metabolic switch from glycolysis to oxidative phosphorylation and glutamine metabolism that occurs during early HFSC lineage progression. HFSC fate reversibility and glutamine metabolism are regulated by the mammalian target of rapamycin complex 2 (mTORC2)-Akt signaling axis within the niche. Deletion of mTORC2 results in a failure to re-establish the HFSC niche, defective hair follicle regeneration, and compromised long-term maintenance of HFSCs. These findings highlight the importance of spatiotemporal control of SC metabolic states in organ homeostasis.*

Role of syndecan-1 in the interaction between dendritic cells and T cells.

Kouwenberg M, Rops A, Bakker-van Bebber M, Diepeveen L, Götte M, Hilbrands L, van der Vlag J. PLoS One 2020 Jul 23;15(7):e0230835. doi: 10.1371/journal.pone.0230835.

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Abstract: *Syndecan-1 (Sdc-1) is a heparan sulfate proteoglycan that can bind cytokines and chemokines via its heparan sulfate side chains, and has immunomodulatory properties in experimental models. Sdc-1 expression has been reported on dendritic cells (DC) and T cells. The potential role of Sdc-1 in DC-T cell interaction has not been investigated yet. We postulate that Sdc-1 is involved in DC-T cell interaction and may influence graft survival in an allogeneic transplant model. Sdc-1 expression on bone marrow-derived DC and T cells was analyzed by flow cytometry. Unstimulated and LPS stimulated Sdc-1 deficient DC were evaluated in vitro for phenotype and stimulatory capacity in mixed lymphocyte reaction. Sdc-1 deficient T cells were evaluated for proliferative capacity and differentiation in a mixed lymphocyte reaction and a proliferation assay. Allograft survival was evaluated in a fully MHC mismatched heterotopic heart transplant model, with either Sdc-1 deficient donors or recipients. Sdc-1 was expressed on the cell surface of unstimulated and LPS matured DC. Sdc-1 deficiency had no effect on expression of co-stimulatory molecules, cytokine production or T cell stimulatory capacity as compared to WT DC. Sdc-1 expression was not detectable on WT T cells, although intracellular Sdc-1 expression could be demonstrated after ConA activation. Sdc-1 deficient T cells showed reduced proliferation upon DC or ConA stimulation and reduced IL-17 production upon ConA stimulation, compared to WT T cells. Sdc-1 deficiency of either allograft or recipient did not prolong allograft survival. In conclusion, Sdc-1 is expressed on the cell surface of DC, where its absence does not affect DC phenotype or T cell stimulatory capacity. Sdc-1 is intracellularly expressed in ConA activated T cells. Sdc-1 deficiency in T cells results in a reduced proliferative response in vitro, as induced by DC and ConA. Sdc-1 deficiency in donor or recipient does not affect allograft survival.*

Initial WNT/β-Catenin Activation Enhanced Mesoderm Commitment, Extracellular Matrix Expression, Cell Aggregation and Cartilage Tissue Yield From Induced Pluripotent Stem Cells.

Kreuser U, Buchert J, Haase A, Richter W, Diederichs S. Front Cell Dev Biol. 2020 Oct 30;8:581331. doi: 10.3389/fcell.2020.581331.

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Abstract: *Mesodermal differentiation of induced pluripotent stem cells (iPSCs) in vitro and subsequent specification into mesodermal derivatives like chondrocytes is currently afflicted with a substantial cell loss that severely limits tissue yield. More knowledge on the key players regulating mesodermal differentiation of iPSCs is currently needed to drive all cells into the desired lineage and to overcome the current need for intermediate cell selection steps to remove misdifferentiated cells. Using two independent human iPSC lines, we here report that a short initial WNT/β-catenin pulse induced by the small molecule CHIR99021 (24 h) enhanced expression of mesodermal markers (PDGFRα, HAND1, KDR, and GATA4), supported the exit from pluripotency (decreased OCT4, SOX2, and LIN28A) and inhibited ectodermal misdifferentiation (reduced PAX6, TUBB3, and NES). Importantly, the initial CHIR pulse increased cell proliferation until day 14 (five-fold), adjusted expression of adhesion-related genes (CDH3 up, CDH6 down) and increased extracellular matrix (ECM)-related gene expression (COL6, COL1, COL3, COL5, DCN, NPNT, LUM, MGP, MATN2, and VTN), thus yielding more matrix-interacting progenitors with a high aggregation capability. Enhanced contribution to chondrogenic pellet formation increased the cell yield after eight weeks 200-fold compared to controls. The collagen type II and proteoglycan-positive area was enlarged in the CHIR group, indicating an increased number of cartilage-forming cells. Conclusively, short initial WNT activation improved mesoderm commitment and our data demonstrated for the first time to our knowledge that, acting via stimulation of cell proliferation, ECM expression and cell aggregation, WNT pulsing is a key step to make cell selection steps before chondrogenesis obsolete. This advanced understanding of the WNT/β-catenin function is a major step toward robust and efficient generation of high-quality mesodermal progenitors from human iPSCs and toward rescuing low tissue yield during subsequent in vitro chondrogenesis, which is highly desired for clinical cartilage regeneration, disease modeling and drug screening.*

Prognostic significance of hedgehog signaling network-related gene expression in breast cancer patients.
Kuehn J, Espinoza-Sanchez NA, Teixeira FCOB, Pavão MSG, Kiesel L, Győrffy B, Greve B, Götte M. J Cell Biochem. 2021 Jan 8. doi: 10.1002/jcb.29886.
Corresponding author: mgotte@uni-muenster.de
Abstract: *Breast cancer continues to be a serious public health problem. The role of the hedgehog pathway in normal development of the mammary gland as well as in carcinogenesis and progression of breast cancer is the subject of intense investigation, revealing functional interactions with cell surface heparan sulfate. Nevertheless, its influence on breast cancer prognosis, and its relation to specific sulfation motifs in heparan sulfate have only been poorly studied in large patient cohorts. Using the public database KMplotter that includes gene expression and survival data of 3951 patients, we found that the higher expression of SHH, HHAT, PTCH1, GLI1, GLI2, and GLI3 positively influences breast cancer prognosis. Stratifying patients according to the expression of hormone receptors, histological grade, lymph node metastasis, and systemic therapy, we observed that GLI1, GLI2, and GLI3 expression, as well as co-expression of SHH and ELP1 were associated with worse relapse-free survival in patients with HER2-positive tumors. Moreover, GLI1 expression in progesterone receptor-negative tumors and GLI3 expression in grade 3 tumors correlated with poor prognosis. SHH, in a panel of cell lines representing different breast cancer subtypes, and HHAT, PTCH1, GLI1, GLI2, and GLI3 were mostly expressed in cell lines classified as HER2-positive and basal-like. Expression of SHH, HHAT, GLI2, and GLI3 was differentially affected by overexpression of the heparan sulfate sulfotransferases HS2ST1 and HS3ST2 in vitro. Although high HS2ST1 expression was associated with poor prognosis in KMplotter analysis, high levels of HS3ST2 were associated with a good prognosis, except for ER-positive breast cancer. We suggest the GLI transcription factors as possible markers for the diagnosis, treatment, and prognosis of breast cancer especially in HER2-positive tumors, but also in progesterone receptor-negative and grade-3 tumors. The pathway interaction and prognostic impact of specific heparan sulfate sulfotransferases provide novel perspectives regarding a therapeutical targeting of the hedgehog pathway in breast cancer.*

Optical Tweezers Approaches for Probing Multiscale Protein Mechanics and Assembly.
Lehmann K, Shayegan M, Blab GA, Forde NR. Front Mol Biosci. 2020 Oct 6;7:577314. doi: 10.3389/fmolb.2020.577314.
Corresponding author: nforde@sfu.ca
Abstract: *Multi-step assembly of individual protein building blocks is key to the formation of essential higher-order structures inside and outside of cells. Optical tweezers is a technique well suited to investigate the mechanics and dynamics of these structures at a variety of size scales. In this mini-review, we highlight experiments that have used optical tweezers to investigate protein assembly and mechanics, with a focus on the extracellular matrix protein collagen. These examples demonstrate how optical tweezers can be used to study mechanics across length scales, ranging from the single-molecule level to fibrils to protein networks. We discuss challenges in experimental design and interpretation, opportunities for integration with other experimental modalities, and applications of optical tweezers to current questions in protein mechanics and assembly.*

Endothelial Basement Membrane Laminins as an Environmental Cue in Monocyte Differentiation to Macrophages. Li L, Song J, Chuquisana O, Hannocks MJ, Loismann S, Vogl T, Roth J, Hallmann R, Sorokin L. Front Immunol. 2020 Oct 30;11:584229. doi: 10.3389/fimmu.2020.584229.
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Abstract: *Background: Monocyte differentiation to macrophages is triggered by migration across the endothelial barrier, which is constituted by both endothelial cells and their underlying basement membrane. We address here the role of the endothelial basement membrane laminins (laminins 411 and 511) in this monocyte to macrophage switch. Chimeric mice carrying CX3CR1-GFP bone marrow were employed to track CCL2-induced monocyte extravasation in a cremaster muscle model using intravital microscopy, revealing faster extravasation in mice*

lacking endothelial laminin 511 (Tek-cre::Lama5-/-) and slower extravasation in mice lacking laminin 411 (Lama4-/-). CX3CR1-GFPlow extravasating monocytes were found to have a higher motility at laminin 511 low sites and to preferentially exit vessels at these sites. However, in vitro experiments reveal that this is not due to effects of laminin 511 on monocyte migration mode nor on the tightness of the endothelial barrier. Rather, using an intestinal macrophage replenishment model and in vitro differentiation studies, we demonstrate that laminin 511, together with the attached endothelium, promote monocyte differentiation to macrophages. Macrophage differentiation is associated with a change in integrin profile, permitting differentiating macrophages to distinguish between laminin 511 high and low areas and to preferentially migrate across laminin 511 low sites. These studies highlight the endothelial basement membrane as a critical site for monocyte differentiation to macrophages, which may be relevant to the differentiation of other cells at vascular niches.

hBMSC-Derived Extracellular Vesicles Attenuate IL-1β-Induced Catabolic Effects on OA-Chondrocytes by Regulating Pro-inflammatory Signaling Pathways.

Li S, Stöckl S, Lukas C, Götz J, Herrmann M, Federlin M, Grässel S. Front Bioeng Biotechnol. 2020 Dec 14;8:603598. doi: 10.3389/fbioe.2020.603598.

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Abstract: *Human bone marrow-derived mesenchymal stromal cells (hBMSCs) provide a promising therapeutic approach in the cell-based therapy of osteoarthritis (OA). However, several disadvantages evolved recently, including immune responses of the host and regulatory hurdles, making it necessary to search for alternative treatment options. Extracellular vesicles (EVs) are released by multiple cell types and tissues into the extracellular microenvironment, acting as message carriers during intercellular communication. Here, we investigate putative protective effects of hBMSC-derived EVs as a cell-free approach, on IL-1ϐ-stimulated chondrocytes obtained from OA-patients. Methods: EVs were harvested from the cell culture supernatant of hBMSCs by a sequential ultracentrifugation process. Western blot, scanning electron microscopy (SEM), and nanoparticle tracking analysis (NTA) were performed to characterize the purified particles as EVs. Intracellular incorporation of EVs, derived from PHK26-labeled hBMSCs, was tested by adding the labeled EVs to human OA chondrocytes (OA-CH), followed by fluorescence microscopy. Chondrocytes were pre-stimulated with IL-1ϐ for 24 h, followed by EVs treatment for 24 h. Subsequently, proliferation, apoptosis, and migration (wound healing) were analyzed via BrdU assay, caspase 3/7 assay, and scratch assay, respectively. With qRT-PCR, the relative expression level of anabolic and catabolic genes was determined. Furthermore, immunofluorescence microscopy and western blot were performed to evaluate the protein expression and phosphorylation levels of Erk1/2, PI3K/Akt, p38, TAK1, and NF-κB as components of pro-inflammatory signaling pathways in OA-CH. Results: EVs from hBMSCs (hBMSC-EVs) promote proliferation and reduce apoptosis of OA-CH and IL-1ϐ-stimulated OA-CH. Moreover, hBMSC-EVs attenuate IL-1ϐ-induced reduction of chondrocyte migration. Furthermore, hBMSC-EVs increase gene expression of PRG4, BCL2, and ACAN (aggrecan) and decrease gene expression of MMP13, ALPL, and IL1ß in OA-CH. Notably, COL2A1, SOX9, BCL2, ACAN, and COMP gene expression levels were significantly increased in IL-1ϐ+ EV groups compared with those IL-1ϐ groups without EVs, whereas the gene expression levels of COLX, IL1B, MMP13, and ALPL were significantly decreased in IL-1ϐ+ EV groups compared to IL-1ϐ groups without EVs. In addition, the phosphorylation status of Erk1/2, PI3K/Akt, p38, TAK1, and NF-κB signaling molecules, induced by IL-1ϐ, is prevented by hBMSC- EVs. Conclusion: EVs derived from hBMSCs alleviated IL-1ϐ-induced catabolic effects on OA-CH via promoting proliferation and migration and reducing apoptosis, probably via downregulation of IL-1ß-activated pro-inflammatory Erk1/2, PI3K/Akt, p38, TAK1, and NF-κB signaling pathways. EVs released from BMSCs may be considered as promising cell-free intervention strategy in cartilage regenerative medicine, avoiding several adverse effects of cell-based regenerative approaches.*

Thiol switches in membrane proteins - Extracellular redox regulation in cell biology.
Lorenzen I, Eble JA, Hanschmann EM. Biol Chem. 2020 Oct 28:/j/bchm.ahead-of-print/hsz-2020-0266/hsz-2020-0266.xml. doi: 10.1515/hsz-2020-0266.
Corresponding author: ilorenzen@zbm.uni-kiel.de and johannes.eble@uni-muenster.de and eva-maria.hanschmann@med.uni-duesseldorf.de
Abstract: *Background: Redox-mediated signal transduction depends on the enzymatic production of second messengers such as hydrogen peroxide, nitric oxide and hydrogen sulfite, as well as specific, reversible redox modifications of cysteine-residues in proteins. So-called thiol switches induce for instance conformational changes in specific proteins that regulate cellular pathways e.g., cell metabolism, proliferation, migration, gene expression and inflammation. Reduction, oxidation and disulfide isomerization are controlled by oxidoreductases of the thioredoxin family, including thioredoxins, glutaredoxins, peroxiredoxins and protein dsisulfide isomerases. These proteins are located in different cellular compartments, interact with substrates and catalyze specific reactions. Interestingly, some of these proteins are released by cells. Their extracellular functions and generally extracellular redox control have been widely underestimated. Here, we give an insight into extracellular redox signaling, extracellular thiol switches and their regulation by secreted oxidoreductases and thiol-isomerases, a topic whose importance has been scarcely studied so far, likely due to methodological limitations. We focus on the secreted redox proteins and characterized thiol switches in the ectodomains of membrane proteins, such as integrins and the metalloprotease ADAM17, which are among the best-characterized proteins and discuss their underlying mechanisms and biological implications.*

MiR-218 affects hypertrophic differentiation of human mesenchymal stromal cells during chondrogenesis via targeting RUNX2, MEF2C, and COL10A1.
Melnik S, Gabler J, Dreher SI, Hecht N, Hofmann N, Großner T, Richter W. Stem Cell Res Ther. 2020 Dec 10;11(1):532. doi: 10.1186/s13287-020-02026-6.
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Abstract: *Background: Human mesenchymal stromal cells (MSC) hold hopes for cartilage regenerative therapy due to their chondrogenic differentiation potential. However, undesirable occurrence of calcification after ectopic transplantation, known as hypertrophic degeneration, remains the major obstacle limiting application of MSC in cartilage tissue regeneration approaches. There is growing evidence that microRNAs (miRs) play essential roles in post-transcriptional regulation of hypertrophic differentiation during chondrogenesis. Aim of the study was to identify new miR candidates involved in repression of hypertrophy-related targets. Methods: The miR expression profile in human articular chondrocytes (AC) was compared to that in hypertrophic chondrocytes derived from human MSC by microarray analysis, and miR expression was validated by qPCR. Putative targets were searched by in silico analysis and validated by miR reporter assay in HEK293T, by functional assays (western blotting and ALP-activity) in transiently transfected SaOS-2 cells, and by a miR pulldown assay in human MSC. The expression profile of miR-218 was assessed by qPCR during in vitro chondrogenesis of MSC and re-differentiation of AC. MSC were transfected with miR-218 mimic, and differentiation outcome was assessed over 28 days. MiR-218 expression was quantified in healthy and osteoarthritic cartilage of patients. Results: Within the top 15 miRs differentially expressed between chondral AC versus endochondral MSC differentiation, miR-218 was selected as a candidate miR predicted to target hypertrophy-related genes. MiR-218 was downregulated during chondrogenesis of MSC and showed a negative correlation to hypertrophic markers, such as COL10A1 and MEF2C. It was confirmed in SaOS-2 cells that miR-218 directly targets hypertrophy-related COL10A1, MEF2C, and RUNX2, as a gain of ectopic miR-218 mimic caused drop in MEF2C and RUNX2 protein accumulation, with attenuation of COL10A1 expression and significant concomitant reduction of ALP activity. A miR pulldown assay confirmed that miR-218 directly targets RUNX2, MEF2C in human MSC. Additionally, the gain of miR-218 in human MSC attenuated hypertrophic markers (MEF2C, RUNX2, COL10A1, ALPL), although with no boost of chondrogenic markers (GAG deposition, COL2A1) due to activation of*

WNT/β-catenin signaling. Moreover, no correlation between miR-218 expression and a pathologic phenotype in the cartilage of osteoarthritis (OA) patients was found. Conclusions: Although miR-218 was shown to target pro-hypertrophic markers MEF2C, COL10A1, and RUNX2 in human MSC during chondrogenic differentiation, overall, it could not significantly reduce the hypertrophic phenotype or boost chondrogenesis. This could be explained by a concomitant activation of WNT/β-catenin signaling counteracting the anti-hypertrophic effects of miR-218. Therefore, to achieve a full inhibition of the endochondral pathway, a whole class of anti-hypertrophic miRs, including miR-218, needs to be taken into consideration.

The Polyphenol Pterostilbene Ameliorates the Myopathic Phenotype of Collagen VI Deficient Mice via Autophagy Induction.

Metti S, Gambarotto L, Chrisam M, Baraldo M, Braghetta P, Blaauw B, Bonaldo P. Front Cell Dev Biol. 2020 Sep 29;8:580933. doi: 10.3389/fcell.2020.580933.

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Abstract: *The induction of autophagy, the catabolic pathway by which damaged or unnecessary cellular components are subjected to lysosome-mediated degradation and recycling, is impaired in Collagen VI (COL6) null mice and COL6-related myopathies. This autophagic impairment causes an accumulation of dysfunctional mitochondria, which in turn leads to myofiber degeneration. Our previous work showed that reactivation of autophagy in COL6-related myopathies is beneficial for muscle structure and function both in the animal model and in patients. Here we show that pterostilbene (Pt)-a non-toxic polyphenol, chemically similar to resveratrol but with a higher bioavailability and metabolic stability-strongly promotes in vivo autophagic flux in the skeletal muscle of both wild-type and COL6 null mice. Reactivation of autophagy in COL6-deficient muscles was also paralleled by several beneficial effects, including significantly decreased incidence of spontaneous apoptosis, recovery of ultrastructural defects and muscle remodeling. These findings point at Pt as an effective autophagy-inducing nutraceutical for skeletal muscle with great potential in counteracting the major pathogenic hallmarks of COL6-related myopathies, a valuable feature that may be also beneficial in other muscle pathologies characterized by defective regulation of the autophagic machinery.*

Infrared Microspectroscopy and Imaging Analysis of Inflammatory and Non-Inflammatory Breast Cancer Cells and Their GAG Secretome.

Mohamed HT, Untereiner V, Cinque G, Ibrahim SA, Götte M, Nguyen NQ, Rivet R, Sockalingum GD, Brézillon S. Molecules. 2020 Sep 19;25(18):4300. doi: 10.3390/molecules25184300.

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Abstract: *Glycosaminoglycans (GAGs)/proteoglycans (PGs) play a pivotal role in the metastasis of inflammatory breast cancer (IBC). They represent biomarkers and targets in diagnosis and treatment of different cancers including breast cancer. Thus, GAGs/PGs could represent potential prognostic/diagnostic biomarkers for IBC. In the present study, non-IBC MDA-MB-231, MCF7, SKBR3 cells and IBC SUM149 cells, as well as their GAG secretome were analyzed. The latter was measured in toto as dried drops with high-throughput (HT) Fourier Transform InfraRed (FTIR) spectroscopy and imaging. FTIR imaging was also employed to investigate single whole breast cancer cells while synchrotron-FTIR microspectroscopy was used to specifically target their cytoplasms. Data were analyzed by hierarchical cluster analysis and principal components analysis. Results obtained from HT-FTIR analysis of GAG drops showed that the inter-group variability enabled us to delineate between cell types in the GAG absorption range 1350-800 cm-1. Similar results were obtained for FTIR imaging of GAG extracts and fixed single whole cells. Synchrotron-FTIR data from cytoplasms allowed discrimination between non-IBC and IBC. Thus, by using GAG specific region, not only different breast cancer cell lines could be differentiated, but also non-IBC from IBC cells. This could be a potential diagnostic spectral marker for IBC detection useful for patient management.*

Influence of Extracellular Vesicles Isolated From Osteoblasts of Patients With Cox-Arthrosis and/or Osteoporosis on Metabolism and Osteogenic Differentiation of BMSCs.

Niedermair T, Lukas C, Li S, Stöckl S, Craiovan B, Brochhausen C, Federlin M, Herrmann M, Grässel S. Front Bioeng Biotechnol. 2020 Dec 23;8:615520. doi: 10.3389/fbioe.2020.615520.

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Abstract: *Background: Studies with extracellular vesicles (EVs), including exosomes, isolated from mesenchymal stem cells (MSC) indicate benefits for the treatment of musculoskeletal pathologies as osteoarthritis (OA) and osteoporosis (OP). However, little is known about intercellular effects of EVs derived from pathologically altered cells that might influence the outcome by counteracting effects from "healthy" MSC derived EVs. We hypothesize, that EVs isolated from osteoblasts of patients with hip OA (coxarthrosis/CA), osteoporosis (OP), or a combination of both (CA/OP) might negatively affect metabolism and osteogenic differentiation of bone-marrow derived (B)MSCs. Methods: Osteoblasts, isolated from bone explants of CA, OP, and CA/OP patients, were compared regarding growth, viability, and osteogenic differentiation capacity. Structural features of bone explants were analyzed via µCT. EVs were isolated from supernatant of naïve BMSCs and CA, OP, and CA/OP osteoblasts (osteogenic culture for 35 days). BMSC cultures were stimulated with EVs and subsequently, cell metabolism, osteogenic marker gene expression, and osteogenic differentiation were analyzed. Results: Trabecular bone structure was different between the three groups with lowest number and highest separation in the CA/OP group. Viability and Alizarin red staining increased over culture time in CA/OP osteoblasts whereas growth of osteoblasts was comparable. Alizarin red staining was by trend higher in CA compared to OP osteoblasts after 35 days and ALP activity was higher after 28 and 35 days. Stimulation of BMSC cultures with CA, OP, and CA/OP EVs did not affect proliferation but increased caspase 3/7-activity compared to unstimulated BMSCs. BMSC viability was reduced after stimulation with CA and CA/OP EVs compared to unstimulated BMSCs or stimulation with OP EVs. ALP gene expression and activity were reduced in BMSCs after stimulation with CA, OP, and CA/OP EVs. Stimulation of BMSCs with CA EVs reduced Alizarin Red staining by trend. Conclusion: Stimulation of BMSCs with EVs isolated from CA, OP, and CA/OP osteoblasts had mostly catabolic effects on cell metabolism and osteogenic differentiation irrespective of donor pathology and reflect the impact of tissue microenvironment on cell metabolism. These catabolic effects are important for understanding differences in effects of EVs on target tissues/cells when harnessing them as therapeutic drugs.*

Integrin- and MMP-Mediated Cell-Matrix Interactions in the Tumor Microenvironment.

Niland S, Eble JA. Hold on or Cut? Int J Mol Sci. 2020 Dec 28;22(1):238. doi: 10.3390/ijms22010238.

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Abstract: *The tumor microenvironment (TME) has become the focus of interest in cancer research and treatment. It includes the extracellular matrix (ECM) and ECM-modifying enzymes that are secreted by cancer and neighboring cells. The ECM serves both to anchor the tumor cells embedded in it and as a means of communication between the various cellular and non-cellular components of the TME. The cells of the TME modify their surrounding cancer-characteristic ECM. This in turn provides feedback to them via cellular receptors, thereby regulating, together with cytokines and exosomes, differentiation processes as well as tumor progression and spread. Matrix remodeling is accomplished by altering the repertoire of ECM components and by biophysical changes in stiffness and tension caused by ECM-crosslinking and ECM-degrading enzymes, in particular matrix metalloproteinases (MMPs). These can degrade ECM barriers or, by partial proteolysis, release soluble ECM fragments called matrikines, which influence cells inside and outside the TME. This review examines the changes in the ECM of the TME and the interaction between cells and the ECM, with a particular focus on MMPs.*

Multiscale Analysis of Extracellular Matrix Remodeling in the Failing Heart.
Perestrelo AR, Silva AC, Oliver-De La Cruz J, Martino F, Horváth V, Caluori G, Polanský O, Vinarský V, Azzato G, de Marco G, Žampachová V, Skládal P, Pagliari S, Rainer A, Pinto-do-Ó P, Caravella A, Koci K, Nascimento DS, Forte G. Circ Res. 2021 Jan 8;128(1):24-38. doi: 10.1161/CIRCRESAHA.120.317685.
Corresponding author: chloe.yeung@gmail.com
Abstract: *Rationale: Cardiac ECM (extracellular matrix) comprises a dynamic molecular network providing structural support to heart tissue function. Understanding the impact of ECM remodeling on cardiac cells during heart failure (HF) is essential to prevent adverse ventricular remodeling and restore organ functionality in affected patients. Objectives: We aimed to (1) identify consistent modifications to cardiac ECM structure and mechanics that contribute to HF and (2) determine the underlying molecular mechanisms. Methods and results: We first performed decellularization of human and murine ECM (decellularized ECM) and then analyzed the pathological changes occurring in decellularized ECM during HF by atomic force microscopy, 2-photon microscopy, high-resolution 3-dimensional image analysis, and computational fluid dynamics simulation. We then performed molecular and functional assays in patient-derived cardiac fibroblasts based on YAP (yes-associated protein)-transcriptional enhanced associate domain (TEAD) mechanosensing activity and collagen contraction assays. The analysis of HF decellularized ECM resulting from ischemic or dilated cardiomyopathy, as well as from mouse infarcted tissue, identified a common pattern of modifications in their 3-dimensional topography. As compared with healthy heart, HF ECM exhibited aligned, flat, and compact fiber bundles, with reduced elasticity and organizational complexity. At the molecular level, RNA sequencing of HF cardiac fibroblasts highlighted the overrepresentation of dysregulated genes involved in ECM organization, or being connected to TGFβ1 (transforming growth factor β1), interleukin-1, TNF-α, and BDNF signaling pathways. Functional tests performed on HF cardiac fibroblasts pointed at mechanosensor YAP as a key player in ECM remodeling in the diseased heart via transcriptional activation of focal adhesion assembly. Finally, in vitro experiments clarified pathological cardiac ECM prevents cell homing, thus providing further hints to identify a possible window of action for cell therapy in cardiac diseases. Conclusions: Our multiparametric approach has highlighted repercussions of ECM remodeling on cell homing, cardiac fibroblast activation, and focal adhesion protein expression via hyperactivated YAP signaling during HF.*

Syndecan-1 modulates the invasive potential of endometrioma via TGF-β signalling in a subgroup of women with endometriosis.
Ponandai-Srinivasan S, Saare M, Boggavarapu NR, Frisendahl C, Ehrström S, Riethmüller C, García-Uribe PA, Rettkowski J, Iyengar A, Salumets A, Lalitkumar PGL, Götte M, Gemzell-Danielsson K. Hum Reprod. 2020 Oct 1;35(10):2280-2293. doi: 10.1093/humrep/deaa164.
Corresponding author: sakthi.ponandaisrinivasan@ki.se
Abstract: *Study question: What is the physiological role of transforming growth factor-beta (TGF-β1) and syndecans (SDC1, SDC4) in endometriotic cells in women with endometriosis? Summary answer: We observed an abnormal, pro-invasive phenotype in a subgroup of samples with ovarian endometriosis, which was reversed by combining gene silencing of SDC1 with the TGF-β1 treatment. What is known already: Women with endometriosis express high levels of TGF-β1 and the proteoglycan co-receptors SDC1 and SDC4 within endometriotic cysts. However, how SDC1 and SDC4 expression is regulated by TGF-β1 and the physiological significance of the high expression in endometriotic cysts remains unknown as does the potential role in disease severity. Study design, size, duration: We utilized a pre-validated panel of stem- and cancer cell-associated markers on endometriotic tissue (n = 15) to stratify subgroups of women with endometriosis. Furthermore, CD90+CD73+CD105+ (SC+) endometriotic stromal cells from these patient subgroups were explored for their invasive behaviour in vitro by transient gene inhibition of SDC1 or SDC4, both in the presence or absence of TGF-β1 treatment. Participants/materials, setting, methods: Endometriotic cyst biopsies (n = 15) were obtained from women diagnosed with ovarian endometriosis (ASRM Stage III-IV). Gene expression variability was assessed on tissue samples by applying gene clustering tools for the dataset generated*

from the pre-validated panel of markers. Three-dimensional (3D) spheroids from endometriotic SC+ were treated in vitro with increasing doses of TGF-β1 or the TGFBRI/II inhibitor Ly2109761 and assessed for SDC1, SDC4 expression and in vitro 3D-spheroid invasion. Transcriptomic signatures from the invaded 3D spheroids were evaluated upon combining transient gene silencing of SDC1 or SDC4, both in presence or absence of TGF-β1 treatment. Furthermore, nanoscale changes on the surface of endometriotic cells were analysed after treatment with TGF-β1 or TGFBRI/II inhibitor using atomic force microscopy. Main results and the role of chance: Gene clustering analysis revealed that endometriotic tissues displayed variability in their gene expression patterns; a small subgroup of samples (2/15, Endo-hi) exhibited high levels of SDC1, SDC4 and molecules involved in TGF-β signalling (TGF-β1, ESR1, CTNNB1, SNAI1, BMI1). The remaining endometriotic samples (Endo-lo) showed a uniform, low gene expression profile. Three-dimensional spheroids derived from Endo-hi SC+ but not Endo-lo SC+ samples showed an aberrant expression of SDC1 and exhibited enhanced 3D-spheroid invasion in vitro, upon rhTGF-β1 treatment. However, this abnormal, pro-invasive response of Endo-hi SC+ was reversed upon gene silencing of SDC1 with the TGF-β1 treatment. Interestingly, transcriptomic signatures of 3D spheroids silenced for SDC1 and consecutively treated with TGF-β1, showed a down-regulation of cancer-associated pathways such as WNT and GPCR signalling. Large scale data: Transcriptomic data were deposited in NCBI's Gene Expression Omnibus (GEO) and could be retrieved using GEO series accession number: GSE135122. Limitations, reasons for caution: It is estimated that about 2.5% of endometriosis patients have a potential risk for developing ovarian cancer later in life. It is possible that the pro-oncogenic molecular changes observed in this cohort of endometriotic samples may not correlate with clinical occurrence of ovarian cancer later in life, thus a validation will be required. Wider implications of the findings: This study emphasizes the importance of interactions between syndecans and TGF-β1 in the pathophysiology of endometriosis. We believe that this knowledge could be important in order to better understand endometriosis-associated complications such as ovarian cancer or infertility.

ER stress-induced cell death in osteoarthritic cartilage.

Rellmann Y, Eidhof E, Dreier R. Cell Signal. 2021 Feb;78:109880. doi: 10.1016/j.cellsig.2020.109880.

Corresponding author: dreierr@uni-muenster.de

Abstract: *In cartilage, chondrocytes are responsible for the biogenesis and maintenance of the extracellular matrix (ECM) composed of proteins, glycoproteins and proteoglycans. Various cellular stresses, such as hypoxia, nutrient deprivation, oxidative stress or the accumulation of advanced glycation end products (AGEs) during aging, but also translational errors or mutations in cartilage components or chaperone proteins affect the synthesis and secretion of ECM proteins, causing protein aggregates to accumulate in the endoplasmic reticulum (ER). This condition, referred to as ER stress, interferes with cartilage cell homeostasis and initiates the unfolded protein response (UPR), a rescue mechanism to regain cell viability and function. Chronic or irreversible ER stress, however, triggers UPR-initiated cell death. Due to unresolved ER stress in chondrocytes, diseases of the skeletal system, such as chondrodysplasias, arise. ER stress has also been identified as a contributing factor to the pathogenesis of cartilage degeneration processes such as osteoarthritis (OA). This review provides current knowledge about the biogenesis of ECM components in chondrocytes, describes possible causes for the impairment of involved processes and focuses on the ER stress-induced cell death in articular cartilage during OA. Targeting of the ER stress itself or intervention in UPR signaling to reduce death of chondrocytes may be promising for future osteoarthritis therapy.*

ER-resident oxidoreductases are glycosylated and trafficked to the cell surface to promote matrix degradation by tumour cells.

Ros M, Nguyen AT, Chia J, Le Tran S, Le Guezennec X, McDowall R, Vakhrushev S, Clausen H, Humphries MJ, Saltel F, Bard FA. Nat Cell Biol. 2020 Nov;22(11):1371-1381. doi: 10.1038/s41556-020-00590-w.

Corresponding author: fbard@imcb.a-star.edu.sg

Abstract: *Tumour growth and invasiveness require extracellular matrix (ECM) degradation and are stimulated by the GALA pathway, which induces protein O-glycosylation in the endoplasmic reticulum (ER). ECM degradation requires metalloproteases, but whether other enzymes are required is unclear. Here, we show that GALA induces the glycosylation of the ER-resident calnexin (Cnx) in breast and liver cancer. Glycosylated Cnx and its partner ERp57 are trafficked to invadosomes, which are sites of ECM degradation. We find that disulfide bridges are abundant in connective and liver ECM. Cell surface Cnx-ERp57 complexes reduce these extracellular disulfide bonds and are essential for ECM degradation. In vivo, liver cancer cells but not hepatocytes display cell surface Cnx. Liver tumour growth and lung metastasis of breast and liver cancer cells are inhibited by anti-Cnx antibodies. These findings uncover a moonlighting function of Cnx-ERp57 at the cell surface that is essential for ECM breakdown and tumour development.*

SOX9 Knockout Induces Polyploidy and Changes Sensitivity to Tumor Treatment Strategies in a Chondrosarcoma Cell Line.

Stöckl S, Lindner G, Li S, Schuster P, Haferkamp S, Wagner F, Prodinger PM, Multhoff G, Boxberg M, Hillmann A, Bauer RJ, Grässel S. Int J Mol Sci. 2020 Oct 15;21(20):7627. doi: 10.3390/ijms21207627.

Corresponding author: sabine.stoeckl@ukr.de

Abstract: *As most chemotherapeutic drugs are ineffective in the treatment of chondrosarcoma, we studied the expression pattern and function of SOX9, the master transcription factor for chondrogenesis, in chondrosarcoma, to understand the basic molecular principles needed for engineering new targeted therapies. Our study shows an increase in SOX9 expression in chondrosarcoma compared to normal cartilage, but a decrease when the tumors are finally defined as dedifferentiated chondrosarcoma (DDCS). In DDCS, SOX9 is almost completely absent in the non-chondroid, dedifferentiated compartments. CRISPR/Cas9-mediated knockout of SOX9 in a human chondrosarcoma cell line (HTB94) results in reduced proliferation, clonogenicity and migration, accompanied by an inability to activate MMP13. In contrast, adhesion, apoptosis and polyploidy formation are favored after SOX9 deletion, probably involving BCL2 and survivin. The siRNA-mediated SOX9 knockdown partially confirmed these results, suggesting the need for a certain SOX9 threshold for particular cancer-related events. To increase the efficacy of chondrosarcoma therapies, potential therapeutic approaches were analyzed in SOX9 knockout cells. Here, we found an increased impact of doxorubicin, but a reduced sensitivity for oncolytic virus treatment. Our observations present novel insight into the role of SOX9 in chondrosarcoma biology and could thereby help to overcome the obstacle of drug resistance and limited therapy options.*

The heparan sulfate proteoglycan Syndecan-1 influences local bone cell communication via the RANKL/OPG axis.

Timmen M, Hidding H, Götte M, Khassawna TE, Kronenberg D, Stange R. Sci Rep. 2020 Nov 25;10(1):20510. doi: 10.1038/s41598-020-77510-3.

Corresponding author: melanie.timmen@ukmuenster.de

Abstract: *The heparan sulfate proteoglycan Syndecan-1, a mediator of signals between the extracellular matrix and cells involved is able to interact with OPG, one of the major regulators of osteoclastogenesis. The potential of osteoblasts to induce osteoclastogenesis is characterized by a switch of OPG (low osteoclastogenic potential) towards RANKL production (high osteoclastogenic potential). In the present study, we investigated the influence of endogenous Syndecan-1 on local bone-cell-communication via the RANKL/OPG-axis in murine osteoblasts and osteoclasts in wild type and Syndecan-1 lacking cells. Syndecan-1 expression and secretion was increased in osteoblasts with high osteoclastogenic potential. Syndecan-1 deficiency led to increased OPG release by osteoblasts that decreased the availability of RANKL. In co-cultures of Syndecan-1 deficient osteoblasts with osteoclast these increased OPG in supernatant caused decreased development of osteoclasts. Syndecan-1 and RANKL level were increased in serum of aged WT mice, whereas Syndecan-1 deficient mice showed high serum OPG concentration. However, bone structure of Syndecan-1 deficient mice was not different compared to wild type. In conclusion,*

Syndecan-1 could be regarded as a new modulator of bone-cell-communication via RANKL/OPG axis. This might be of high impact during bone regeneration or bone diseases like cancer where Syndecan-1 expression is known to be even more prevalent.

Interaction between KDELR2 and HSP47 as a Key Determinant in Osteogenesis Imperfecta Caused by Bi-allelic Variants in KDELR2.

van Dijk FS, Semler O, Etich J, Köhler A, Jimenez-Estrada JA, Bravenboer N, Claeys L, Riesebos E, Gegic S, Piersma SR, Jimenez CR, Waisfisz Q, Flores CL, Nevado J, Harsevoort AJ, Janus GJM, Franken AAM, van der Sar AM, Meijers-Heijboer H, Heath KE, Lapunzina P, Nikkels PGJ, Santen GWE, Nüchel J, Plomann M, Wagener R, Rehberg M, Hoyer-Kuhn H, Eekhoff EMW, Pals G, Mörgelin M, Newstead S, Wilson BT, Ruiz-Perez VL, Maugeri A, Netzer C, Zaucke F, Micha DAm J Hum Genet. 2020 Nov 5;107(5):989-999. doi: 10.1016/j.ajhg.2020.09.009.

Corresponding author: fleur.dijk@nhs.net and d.micha@amsterdamumc.nl

Abstract: *Osteogenesis imperfecta (OI) is characterized primarily by susceptibility to fractures with or without bone deformation. OI is genetically heterogeneous: over 20 genetic causes are recognized. We identified bi-allelic pathogenic KDELR2 variants as a cause of OI in four families. KDELR2 encodes KDEL endoplasmic reticulum protein retention receptor 2, which recycles ER-resident proteins with a KDEL-like peptide from the cis-Golgi to the ER through COPI retrograde transport. Analysis of patient primary fibroblasts showed intracellular decrease of HSP47 and FKBP65 along with reduced procollagen type I in culture media. Electron microscopy identified an abnormal quality of secreted collagen fibrils with increased amount of HSP47 bound to monomeric and multimeric collagen molecules. Mapping the identified KDELR2 variants onto the crystal structure of G. gallus KDELR2 indicated that these lead to an inactive receptor resulting in impaired KDELR2-mediated Golgi-ER transport. Therefore, in KDELR2-deficient individuals, OI most likely occurs because of the inability of HSP47 to bind KDELR2 and dissociate from collagen type I. Instead, HSP47 remains bound to collagen molecules extracellularly, disrupting fiber formation. This highlights the importance of intracellular recycling of ER-resident molecular chaperones for collagen type I and bone metabolism and a crucial role of HSP47 in the KDELR2-associated pathogenic mechanism leading to OI.*

Imbalanced cellular metabolism compromises cartilage homeostasis and joint function in a mouse model of mucolipidosis type III gamma.

Westermann LM, Fleischhauer L, Vogel J, Jenei-Lanzl Z, Ludwig NF, Schau L, Morellini F, Baranowsky A, Yorgan TA, Di Lorenzo G, Schweizer M, de Souza Pinheiro B, Guarany NR, Sperb-Ludwig F, Visioli F, Oliveira Silva T, Soul J, Hendrickx G, Wiegert JS, Schwartz IVD, Clausen-Schaumann H, Zaucke F, Schinke T, Pohl S, Danyukova T. Dis Model Mech. 2020 Nov 18;13(11):dmm046425. doi: 10.1242/dmm.046425.

Corresponding author: s.pohl@uke.de and t.danyukova@uke.de

Abstract: *Mucolipidosis type III (MLIII) gamma is a rare inherited lysosomal storage disorder caused by mutations in GNPTG encoding the γ-subunit of GlcNAc-1-phosphotransferase, the key enzyme ensuring proper intracellular location of multiple lysosomal enzymes. Patients with MLIII gamma typically present with osteoarthritis and joint stiffness, suggesting cartilage involvement. Using Gnptg knockout (Gnptgko) mice as a model of the human disease, we showed that missorting of a number of lysosomal enzymes is associated with intracellular accumulation of chondroitin sulfate in Gnptgko chondrocytes and their impaired differentiation, as well as with altered microstructure of the cartilage extracellular matrix (ECM). We also demonstrated distinct functional and structural properties of the Achilles tendons isolated from Gnptgko and Gnptab knock-in (Gnptabki) mice, the latter displaying a more severe phenotype resembling mucolipidosis type II (MLII) in humans. Together with comparative analyses of joint mobility in MLII and MLIII patients, these findings provide a basis for better understanding of the molecular reasons leading to joint pathology in these patients. Our data suggest that lack of GlcNAc-1-phosphotransferase activity due to defects in the γ-subunit causes structural changes within the ECM of connective and mechanosensitive tissues, such as cartilage and tendon, and eventually results in functional joint abnormalities*

typically observed in MLIII gamma patients. This idea was supported by a deficit of the limb motor function in Gnptgko mice challenged on a rotarod under fatigue-associated conditions, suggesting that the impaired motor performance of Gnptgko mice was caused by fatigue and/or pain at the joint.This article has an associated First Person interview with the first author of the paper.

Decellularized extracellular matrix scaffolds identify full-length collagen VI as a driver of breast cancer cell invasion in obesity and metastasis.

Wishart AL, Conner SJ, Guarin JR, Fatherree JP, Peng Y, McGinn RA, Crews R, Naber SP, Hunter M, Greenberg AS, Oudin MJ. Sci Adv. 2020 Oct 21;6(43):eabc3175. doi: 10.1126/sciadv.abc3175.

Corresponding author: madeleine.oudin@tufts.edu

Abstract: *The extracellular matrix (ECM), a major component of the tumor microenvironment, promotes local invasion to drive metastasis. Here, we describe a method to study whole-tissue ECM effects from disease states associated with metastasis on tumor cell phenotypes and identify the individual ECM proteins and signaling pathways that are driving these effects. We show that decellularized ECM from tumor-bearing and obese mammary glands drives TNBC cell invasion. Proteomics of the ECM from the obese mammary gland led us to identify full-length collagen VI as a novel driver of TNBC cell invasion whose abundance in tumor stroma increases with body mass index in human TNBC patients. Last, we describe the mechanism by which collagen VI contributes to TNBC cell invasion via NG2-EGFR cross-talk and MAPK signaling. Overall, these studies demonstrate the value of decellularized ECM scaffolds obtained from tissues to identify novel functions of the ECM.*

Proteomics identifies differences in fibrotic potential of extracellular vesicles from human tendon and muscle fibroblasts.

Yeung CC, Schoof EM, Tamáš M, Mackey AL, Kjaer M.Cell Commun Signal. 2020 Nov 4;18(1):177. doi: 10.1186/s12964-020-00669-9.

Corresponding author: chloe.yeung@gmail.com

Abstract: *Background: Fibroblasts are the powerhouses responsible for the production and assembly of extracellular matrix (ECM). Their activity needs to be tightly controlled especially within the musculoskeletal system, where changes to ECM composition affect force transmission and mechanical loading that are required for effective movement of the body. Extracellular vesicles (EVs) are a mode of cell-cell communication within and between tissues, which has been largely characterised in cancer. However, it is unclear what the role of healthy fibroblast-derived EVs is during tissue homeostasis. Methods: Here, we performed proteomic analysis of small EVs derived from primary human muscle and tendon cells to identify the potential functions of healthy fibroblast-derived EVs. Results: Mass spectrometry-based proteomics revealed comprehensive profiles for small EVs released from healthy human fibroblasts from different tissues. We found that fibroblast-derived EVs were more similar than EVs from differentiating myoblasts, but there were significant differences between tendon fibroblast and muscle fibroblast EVs. Small EVs from tendon fibroblasts contained higher levels of proteins that support ECM synthesis, including TGFβ1, and muscle fibroblast EVs contained proteins that support myofiber function and components of the skeletal muscle matrix. Conclusions: Our data demonstrates a marked heterogeneity among healthy fibroblast-derived EVs, indicating shared tasks between EVs of skeletal muscle myoblasts and fibroblasts, whereas tendon fibroblast EVs could play a fibrotic role in human tendon tissue. These findings suggest an important role for EVs in tissue homeostasis of both tendon and skeletal muscle in humans. Video abstract.*

Fluorescence lifetime metabolic mapping of hypoxia-induced damage in pancreatic pseudo-islets. Nidogen-1 Mitigates Ischemia and Promotes Tissue Survival and Regeneration

Zbinden A, Carvajal Berrio DA, Urbanczyk M, Layland SL, Bosch M, Fliri S, Lu CE, Jeyagaran A, Loskill P, Duffy GP, Schenke-Layland K. J Biophotonics. 2020 Dec;13(12):e202000375. doi: 10.1002/jbio.202000375.

Corresponding author: katja.schenke-layland@uni-tuebingen.de
Abstract: *Pancreatic islet isolation from donor pancreases is an essential step for the transplantation of insulin-secreting β-cells as a therapy to treat type 1 diabetes mellitus. This process however damages islet basement membranes, which can lead to islet dysfunction or death. Posttransplantation, islets are further stressed by a hypoxic environment and immune reactions that cause poor engraftment and graft failure. The current standards to assess islet quality before transplantation are destructive procedures, performed on a small islet population that does not reflect the heterogeneity of large isolated islet batches. In this study, we incorporated fluorescence lifetime imaging microscopy (FLIM) into a pancreas-on-chip system to establish a protocol to noninvasively assess the viability and functionality of pancreatic β-cells in a three-dimensional in vitro model (= pseudo-islets). We demonstrate how (pre-) hypoxic β-cell-composed pseudo-islets can be discriminated from healthy functional pseudo-islets according to their FLIM-based metabolic profiles. The use of FLIM during the pretransplantation pancreatic islet selection process has the potential to improve the outcome of β-cell islet transplantation.*

Nidogen-1 Mitigates Ischemia and Promotes Tissue Survival and Regeneration.
Zbinden A, Layland SL, Urbanczyk M, Carvajal Berrio DA, Marzi J, Zauner M, Hammerschmidt A, Brauchle EM, Sudrow K, Fink S, Templin M, Liebscher S, Klein G, Deb A, Duffy GP, Crooks GM, Eble JA, Mikkola HKA, Nsair A, Seifert M, Schenke-Layland K. Adv. Sci. 2020. doi: 10.1002/advs.202002500
Corresponding author: katja.schenke-layland@uni-tuebingen.de
Abstract: *Ischemia impacts multiple organ systems and is the major cause of morbidity and mortality in the developed world. Ischemia disrupts tissue homeostasis, driving cell death, and damages tissue structure integrity. Strategies to heal organs, like the infarcted heart, or to replace cells, as done in pancreatic islet β-cell transplantations, are often hindered by ischemic conditions. Here, it is discovered that the basement membrane glycoprotein nidogen-1 attenuates the apoptotic effect of hypoxia in cardiomyocytes and pancreatic β-cells via the αvβ3 integrin and beneficially modulates immune responses in vitro. It is shown that nidogen-1 significantly increases heart function and angiogenesis, while reducing fibrosis, in a mouse postmyocardial infarction model. These results demonstrate the protective and regenerative potential of nidogen-1 in ischemic conditions.*

Collagen and Endothelial Cell Coculture Improves β-Cell Functionality and Rescues Pancreatic Extracellular Matrix. Zbinden A, Urbanczyk M, Layland SL, Becker L, Marzi J, Bosch M, Loskill P, Duffy GP, Schenke-Layland K. Tissue Eng Part A. 2020 Nov 6. doi: 10.1089/ten.TEA.2020.0250.
Corresponding author: katja.schenke-layland@uni-tuebingen.de
Abstract: *The use of biomaterials and biomaterial functionalization is a promising approach to support pancreatic islet viability posttransplantation in an effort to reduce insulin dependence for patients afflicted with diabetes mellitus type 1. Extracellular matrix (ECM) proteins are known to impact numerous reparative functions in the body. Assessing how endogenously expressed pancreatic ECM proteins are affected by posttransplant-like hypoxic conditions may provide significant insights toward the development of tissue-engineered therapeutic strategies to positively influence β-cell survival, proliferation, and functionality. Here, we investigated the expression of three relevant groups of pancreatic ECM proteins in human native tissue, including basement membrane (BM) proteins (collagen type 4 [COL4], laminins [LAM]), proteoglycans (decorin [DCN], nidogen-1 [NID1]), and fibril-forming proteins (fibronectin [FN], collagen type 1 [COL1]). In an in vitro hypoxia model, we identified that ECM proteins were differently affected by hypoxic conditions, contributing to an overall loss of β-cell functionality. The use of a COL1 hydrogel as carrier material demonstrated a protective effect on β-cells mitigating the effect of hypoxia on proteoglycans as well as fibril-forming protein expression, supporting β-cell functionality in hypoxia. We further showed that providing endothelial cells (ECs) into the COL1 hydrogel improves β-cell response as well as the expression of relevant BM proteins. Our data show that β-cells benefit from a microenvironment composed of structure-providing COL1 with the incorporation of ECs to withstand the harsh conditions of hypoxia. Such hydrogels*

support β-cell survival and can serve as an initial source of ECM proteins to allow cell engraftment while preserving cell functionality posttransplantation. Impact statement Expression analysis identifies hypoxia-induced pathological changes in extracellular matrix (ECM) homeostasis as potential targets to support β-cell transplants by encapsulation in biomaterials for the treatment of diabetes mellitus. A collagen-1 hydrogel is shown to attenuate the effect of hypoxia on β-cells and their ECM expression. The functionalization of the hydrogel with endothelial cells increases the β-cell response to glucose and rescues essential basement membrane proteins.

MATRIX MEETING ANNOUNCEMENTS

#THEmeshwork

At the end of summer, a group of 7 early career researchers (ECRs), including an ISMB board member, initiated a global, informal platform for ECRs (PhD students, postdocs and new PIs) working in the extracellular matrix (ECM) field to:

- Discuss/troubleshoot their ECM research problems
- Connect with each other to make friends and new collaborations worldwide
- Develop their research careers

#THEmeshwork costs nothing to join and all the virtual events are free. We have a messaging platform on Slack where researchers can connect to each other, ask for advice, learn about new publications and new product recommendations. We organise a monthly one-hour online meeting that alternates between scientific sessions and career development sessions.

Scientific sessions are in the relaxed and informal lab-meeting format where two ECRs working on a similar theme give 10-minute presentations, followed by a lively discussion with the attendees led by two established PIs. Our first scientific session took place on 22 October and the theme was “ECM & Cancer”. Julie Di Martino (Icahn School of Medicine at Mount Sinai, USA) and Ines Velazquez Quesada (Temple University, USA) presented their work and Edna Cukierman (The FOX CHASE Cancer Center, USA) and Ryan Petrie (Drexel University) chaired a lively discussion that then continued on the Slack platform. Our last meeting of 2020 took place 17 December and the theme was “ECM & Fibrosis”. Nuno Coelho (St. Michael’s Hospital, Canada) and Joan Chang (Wellcome Trust Centre for Cell-Matrix Research, UK) presented and the chairs were Birgit Leitinger (Imperial College London, UK) and Alexander Nyström (University Freiburg). There were many questions from the 47 attendees and all agreed that the sharing and discussion of exciting, unpublished data in this relaxed format was really engaging!

Career development sessions feature 2-6 new/established PIs or other professionals that give a 3-5-minute introduction and a moderator who drives the discussion on the chosen theme (e.g. grant/funding success, open access, etc) by asking questions from the attendees. Our first career development session was “How to be Successful with Grants” and our expert panel were Abigail Mackey (KU/ISMC), Boris Hinz (University of Toronto), Dan Marenda (Drexel University) and Nicole McNeil Ford (NIH) who imparted lots of useful advice and anecdotes of their experience.

We look forward to welcoming more ISMB members at #THEmeshwork or at our next event on **Thursday 21 January, 4pm - 5pm (Central European Standard time) or 10am – 11 am (Eastern Time) which will be a career development session "Effective communication for delivering an engaging virtual presentation**", featuring speakers Jill K. Gregory, a certified medical illustrator at Mount Sinai (USA), and Eric Snapp from Howards Hughes Medical Institute (USA). https://tinyurl.com/meshworkjan

#THEmeshwork welcomes researchers at all stages and we strongly believe that our network of ECRs benefit from having more established PIs in it! To join, simply email themeshwork2020@gmail.com. To register for the latest event or find out more information, visit our website https://themeshwork2020.wixsite.com/info

#THEmeshwork team are Nuno Coelho, Julie Di Martino, Valerio Izzi, Tia Jones, Pauline Nauroy, Ines Velazquez Quesada, and Chloé Yeung.

2021 ASMB e-Symposium series

Thursday February 11, 2021 - 11am, EST

Fibroblast Cell Phenotypic Changes in Development and Disease

Guest Chair: Morgan Salmon, *University of Virginia School of Medicine*
Summary available at https://asmb.memberclicks.net/e-symposia

Thursday March 11, 2021 - 11am, EST

Matrix Math: Computational Modeling of the ECM

Guest Chair: William Richardson, *Clemson University*

In this "Matrix Math" e-Symposium, we will host cutting-edge talks that utilize computational tools for understanding ECM regulation.

Thursday April 8, 2021 - 11am, EST

Growth factor regulation by extracellular matrices

Guest Chair: Dirk Hubmacher, *Icahn School of Medicine at Mount Sinai*

This ASMB e-Symposium will explore molecular aspects of the regulation of ECM-mediated signaling pathways and the response elicited on a cellular, tissue, or organismal level.
Submission of abstracts from PhD students, postdocs, and junior faculty is highly encouraged.

For more information and abstract submission, visit the ASMB website:
https://asmb.memberclicks.net/e-symposia

The ASMB e-Symposium series is sponsored by:
Matrix Biology and Matrix Biology Plus, published by Elsevier

BRITISH SOCIETY FOR MATRIX BIOLOGY (BMSB) SPRING 2021 MEETING

Inflammation, Fibrosis, Resolution & the Matrix
12th & 13th April 2021
Online Meeting
https://bsmb.ac.uk/meetings/inflammation-fibrosis-resolution-and-matrix/

Chair: Prof Stephanie Dakin

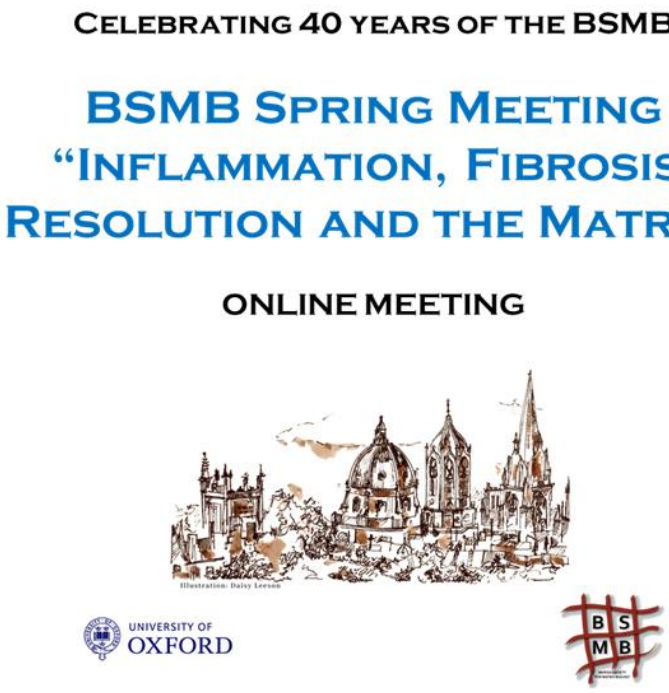
The conference will be held online, fees are £30 for members, £20 for students and £40 for non-members. The meeting will take place over 2 afternoons and will include sessions covering diverse topics, spanning how the matrix is implicated in inflammatory, fibrotic and resolution processes, finishing with translational solutions, together with the Fell-Muir Award Lecture.

Selected abstracts will also be awarded presentation slots in each session to encourage our younger members to engage with the meeting. There will be up to 12 talks awarded to submitted abstracts. Abstracts can be on any topic on inflammation, fibrosis, resolution and the matrix to be selected for an oral presentation. The selection panel will make decisions based upon the quality of the science.

Our host of internationally renowned speakers are already confirmed. This will be a fantastic opportunity to catch up with colleagues and find out the latest cutting-edge developments in this field.

Key dates:

- Registration closes 31st March 2021
- Abstract submission opens on 18th December 2020 and will close on 15th February 2021
- Oral presentation notification 15th March 2021



For further information and to register please visit https://bsmb.ac.uk

Thematic Sessions on Glycosylation and Extracellular Matrix in Development, Repair, and Disease at American Society for Biochemistry and Molecular Biology (ASBMB) 2020 Meeting

Plans are to hold these sessions at the EB2021 meeting in Indianapolis, IN (USA) May 1-4, 2021.

The ASBMB 2020 Meeting should have been held April 4-7 at the San Diego convention center (USA) Along with outstanding award lectures, poster sessions, and workshops, this year six thematic sessions covering foundational areas of biochemistry and molecular biology will meet each of the three mornings of the conference.
One of the themes is entitled, Glycosylation and Extracellular Matrix in Development, Repair, and Disease, co-chaired by Drs. Jamey Marth and Joanne Murphy-Ullrich. They have invited 12 world-class scientists to speak in this three-day theme. Speakers from the ECM community include Lynn Sakai, Joanne Murphy-Ullrich, Kim Midwood, Jeff Esko, Fernando Gomez-Pinilla, and Fei-Fei Liu.

We hope to have many abstracts submitted relevant to glycosylation and extracellular matrix. Additional Spotlight sessions will be added to the program drawn from the submitted abstracts, allowing students, postdoctoral scholars, and other young scientists to present their work orally. Additional abstracts will be chosen for 1 min flash talks, giving the presenter an opportunity to advertise their poster during the morning sessions. Don't miss this opportunity to have your work on the matrix highlighted for the broader ASBMB community! For more details about the conference, see https://www.asbmb.org/meeting2020/

2021 COLLAGEN GORDON RESEARCH SEMINAR

July 10-11, 2021
Colby Sawyer College, NH (USA)
Chairs: Delfien Syx & Jonathan A. Roth
https://www.grc.org/collagen-grs-conference/2021/

2021 COLLAGEN GORDON RESEARCH CONFERENCE

July 11-16, 2021
Colby Sawyer College, NH (USA)
Chair: Taina Pihlajaniemi
Vice Chair: Douglas B. Gould
https://www.grc.org/collagen-conference/2021/

Gordon Research Conferences
Frontiers of Science

Physiological and Disease Relevance and the Underlaying Molecular Properties of Collagens

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

The 2021 Collagen GRS and GRC should be postponed to a later date

2021 ELASTIN, ELASTIC FIBERS AND MICROFIBRILS GORDON RESEARCH SEMINAR

July 24-25, 2021
Southern New Hampshire University, NH (USA)
Chairs: Muthu Lakshmi Muthu & Kirklann N. Lau
https://www.grc.org/elastin-elastic-fibers-and-microfibrils-grs-conference/2021/

2021 ELASTIN, ELASTIC FIBERS AND MICROFIBRILS GORDON RESEARCH CONFERENCE

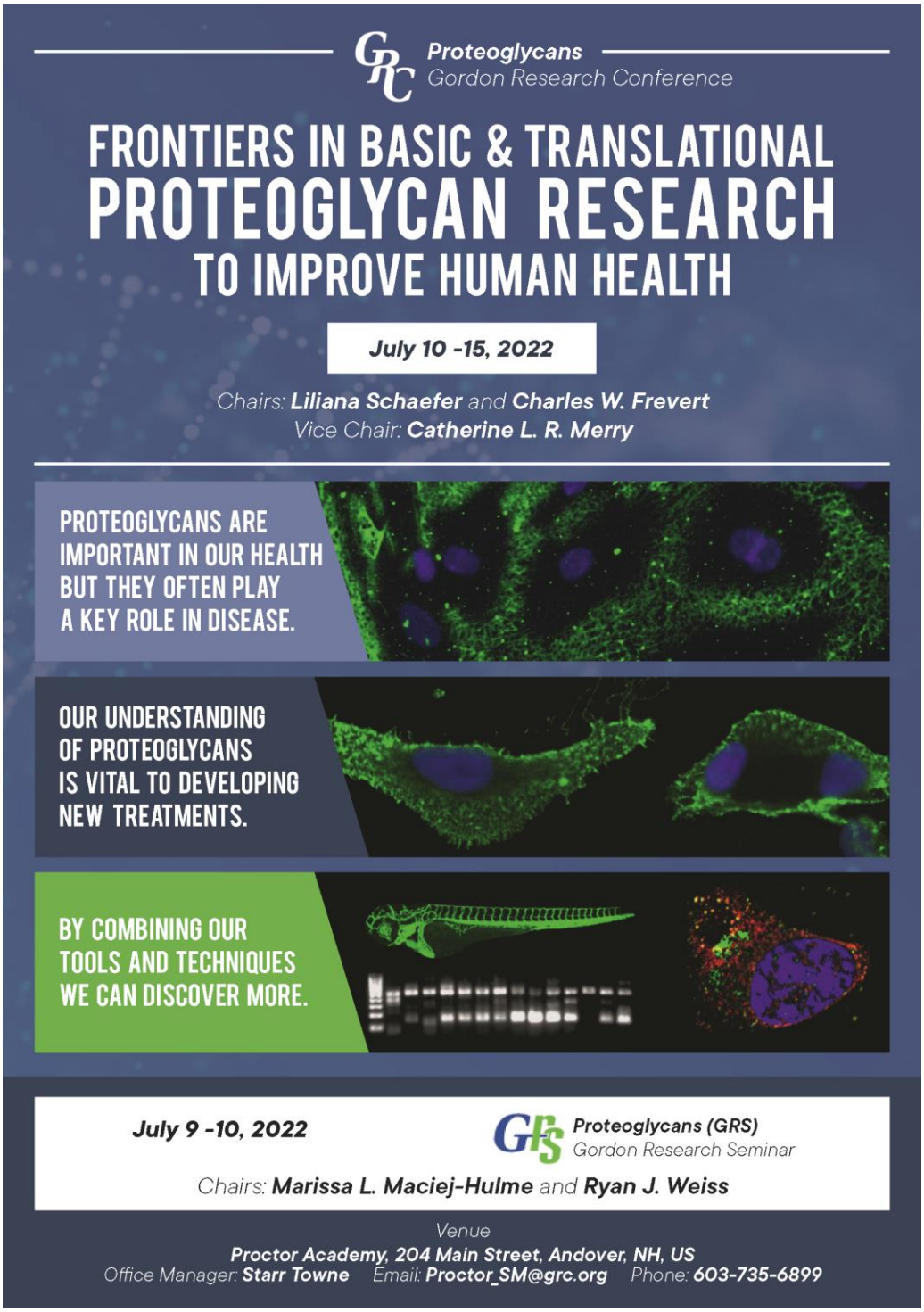
July 25 - 30, 2021
Chair: Dianna Milewicz
Vice Chair: Beth A. Kozel
Southern New Hampshire University, NH (USA)
https://www.grc.org/elastin-elastic-fibers-and-microfibrils-conference/2021/

Gordon Research Conferences
Frontiers of Science

BIENNAL MEETING OF THE AMERICAN SOCIETY FOR MATRIX BIOLOGY

The Matrix In Focus: Matrix, Cells, and Interactions in Health, Disease, Aging, and Regeneration
September 12-15, 2021
Hyatt Regency at the Arch, St. Louis, MO (USA)
Registration and abstract submission will open in March 2021
https://www.asmb.net/2021-biennial-meeting

PROTEOGLYCANS GRS & GRC, JULY 2022, PROCTOR ACADEMY, ANDOVER, NH (USA)

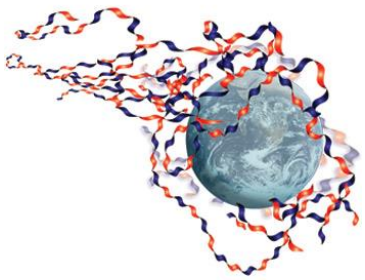


https://www.grc.org/proteoglycans-conference/2022/

IMPORTANT NOTICE on the INTERNATIONAL SOCIETY FOR HYALURONAN SCIENCES (ISHAS) 2023 MEETING

Given the going uncertainty regarding the worldwide COVID-19 situation, we have decided to postpone the HYALURONAN 2021 meeting in Portland, Oregon, until **4-8 June 2023**.

We apologize for any inconvenience caused.



However, **we intend to hold a virtual HA meeting on 15-16 June 2021** and further details on the program and registration will be posted on the ISHAS website in due course: https://www.ishas.org/

Please add these dates to your diaries.