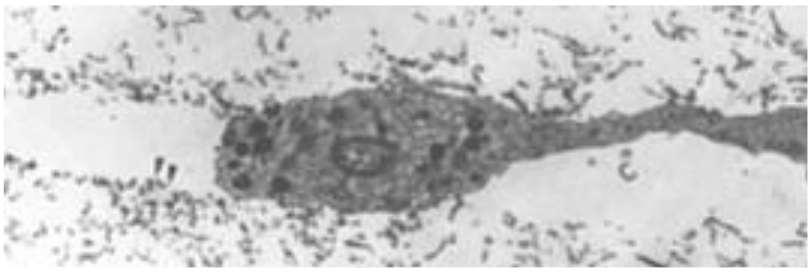

A fibroblast within a tethered lattice, after 13 days, with a cavity surrounding the cell and areas of packed collagen fibrils *(Porter et al. 1998 Wound Rep. Reg. 6: 157-166)*

ISMB NEWSLETTER 36 October 2020 Editor: Sylvie Ricard-Blum

FROM THE PRESIDENT'S DESK

Dear ISMB members,

This issue of the newsletter shows that the extracellular matrix community is dynamic and quick to adapt in different and successful ways to these uncertain and difficult times.

Early career scientists in our field have started a new network (#THEmeshwork), the Pan Pacific Connective Symposium (November 2020) and the Hyaluronan meeting (June 2021) go virtual, whereas the Spring meeting of the British Society for Matrix Biology (Celebrating 40 years BSMB, Oxford, UK, April 2021) and the Collagen Gordon Research Conference (New London, NH, USA, July 2021) should be face-to-face meetings. Several major meetings have been cancelled and postponed to 2021 (the American Society for Matrix Biology meeting) or to 2022 (Matrix Biology Europe meeting and the Proteoglycans GRC) thanks to the tenacity and strong motivation of their organizers.

The ISMB policy on travel awards has been also adapted to these particular circumstances. The executive committee decided in July that all early-career international travel awards made in 2020 will be rescinded, so that funds can be applied to future awards. The awards made in 2020 for cancelled meetings and international travel fellowships will remain listed on the ISMB website. The 2020 Rupert Timpl awardee, Paul Hiebert (ETH, Zürich, Switzerland), could not give his lecture during the MBE meeting but he has been invited to write a review for Matrix Biology Plus thanks to the Editor-in-Chief, Renato Iozzo, and to Elsevier. The ISMB Distinguished Investigator Award 2020 to Bob Mecham (Washington University School of Medicine, St Louis, MO, USA) is postponed to the next ASMB meeting in 2021.

Last, on behalf of the Council and of the ISMB members I warmly thank Jo Adams (University of Bristol, UK) for the excellent job she did when serving as Secretary of the ISMB, and I warmly welcome the new Secretary, John Whitelock (University of New South Wales, Sydney, Australia).

Stay safe, and stay well.
Best wishes.
Sylvie Ricard-Blum, President of the International Society for Matrix Biology (sylvie.ricard-blum@univ-lyon1.fr)

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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Pauline Nauroy (Germany, pauline.nauroy@uniklinik-freiburg.de)
Chloé Yeung (Denmark, chloe.yeung@gmail.com)
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The Swiss Society for Matrix Biology (SSMB)
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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!

A NEW EXTRACELLULAR MATRIX NETWORK

Let's meet THEmeshwork!

Who we are?

THEmeshwork is a global community of matrix researchers which aims to promote and support early career researchers (ECRs). THEmeshwork was created on September 5th by a diverse group of seven ECRs, including PhD students, postdocs, and early PIs and already has more than 130 members!

What's our missions?

Our goal is to provide networking and career development opportunities to ECRs to improve their skills and contribute to the progress of their careers. We encourage ECRs to showcase their work to their peers and more established researchers in a relaxed, lab meeting-like atmosphere. We promote networking and establishment of new collaborations worldwide by connecting ECRs with peers and more experienced researchers in our active Slack platform available to all matrix related researchers. In the Slack we have created dedicated channels for troubleshooting daily matrix research problems as well as promoting matrix research publications and events.

What do we do?

We have created the Slack platform to connect researchers to one another and help ECRs overcome any problem they can encounter. We also organize a monthly online meeting in two distinct formats. Every other month, there is a one-hour scientific event featuring short talks from two ECRs working on the same theme and two invited supportive PIs that will stimulate discussion. In alternating months, there will be a career development event featuring 2 to 6 PIs or invited speakers that will give a short self-introduction and advice on the theme, e.g. success with grants.

How to join?

To sign up simply email us at themeshwork2020@gmail.com! Everybody is welcome in THEmeshwork and sign up is completely free! If you're not an ECR anymore, our community greatly benefits from your wisdom,

knowledge and contacts. We are an open-minded community that accepts everyone at every level, working directly on matrix or matrix-friendly!

How to contribute?

When you sign up, be active on the Slack platform: present yourself, help your colleagues, ask questions, advertise meetings, job offers, etc. Contact us if you want to present during a scientific session and feel free to share any ideas with us - the community will benefit from it! If you are a company or a society, we are looking for sponsors! Email us.

What's next?

Our first scientific event will take place October 22nd, 10 am Eastern time. Julie Di Martino and Ines Velazquez Quesada will talk about matrix and cancer with Edna Cukierman. Our first career development meeting is planned for November 17th, 10 am Eastern time to discuss how to be successful with grants. Stay tuned!

THEmeshwork team

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

OBITUARIES

The extracellular matrix community recently lost two prominent members**. Professor Zena Werb** (University of California, San Francisco, USA) passed away on June 16, 2020. She focused her research on MMPs, and made major contribution on the role of the extracellular environment on breast development.
https://www.ucsf.edu/news/2020/07/417956/scientifically-fearless-cancer-researcher-zena-werb-dies-75
Professor Kazuyuki Sugahara (Meijo University, Nagoya, Japan) passed away on the 29th July. His research interests were centered on glycosaminoglycans and proteoglycans. They will be deeply missed.

MEETING REPORTS

ASMB 2019 Workshop, University of Virginia, Charlottesville, VA (USA) June 23rd-25th 2019
Sent to the ISMB Council in May, 2020

I would like to thank the ISMB for the international travel grant which enabled me to attend the American Society for Matrix Biology (ASMB) 2019 Workshop entitled: "Fibroblasts: The Arbiters of Extracellular Matrix Remodeling". The workshop was held at The University of Virginia, Charlottesville, VA, USA between June 23rd and 25th 2019.
The meeting was split into 8 sessions with topics ranging from fibroblast heterogeneity to extracellular matrix turnover with each group of talks being followed by a panel discussion including all of the speakers from that session. Throughout the meeting there were many interesting discussions on the interactions of fibroblasts, the matrix and immune cells. Among the many highlights of this meeting for me were the excellent talks from Professor Boris Hinz highlighting the crosstalk between the matrix and other cell types and Professor Thomas Barker's

presentation on mechanotransduction. I also had the privilege of giving a short talk about my work in the session: "Fibroblasts and the Reticulum".
The meeting program included 2 scheduled poster sessions and provided many opportunities for discussion of practical and experimental problems as well as deeper discussions on the role of fibroblasts in pathology. Following the oral and poster presentations, I received very valuable feedback. In addition to the in depth discussions, the poster sessions also allowed me to gain a broader understanding of the different work currently being carried out by researchers in the wider fibroblast community.
I also really enjoyed the trainee session that provided an open forum for discussion on working and succeeding within the fibroblast research arena with input from junior researchers to senior scientists. In this session many interesting points were raised and I very much enjoyed the atmosphere that promoted discussion and exchange of ideas.
Attending this meeting was a fantastic opportunity to meet other researchers in the field of fibroblast research and to hopefully build future collaborations. The workshop far exceeded my expectations with outstanding science presented on both days. Once again, I am very grateful to the ISMB for their support and the award of this travel grant and the ASMB meeting organisers for giving me the opportunity to present at such a relevant meeting.

Fiona Kenny, PhD, Research Associate, Stramer Group, King's College London (UK).

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.

WELCOME TO NEW MEMBERS

Ulrich Valcourt, University of Lyon (France)
Kristina Bubb, University of Cologne (Germany)

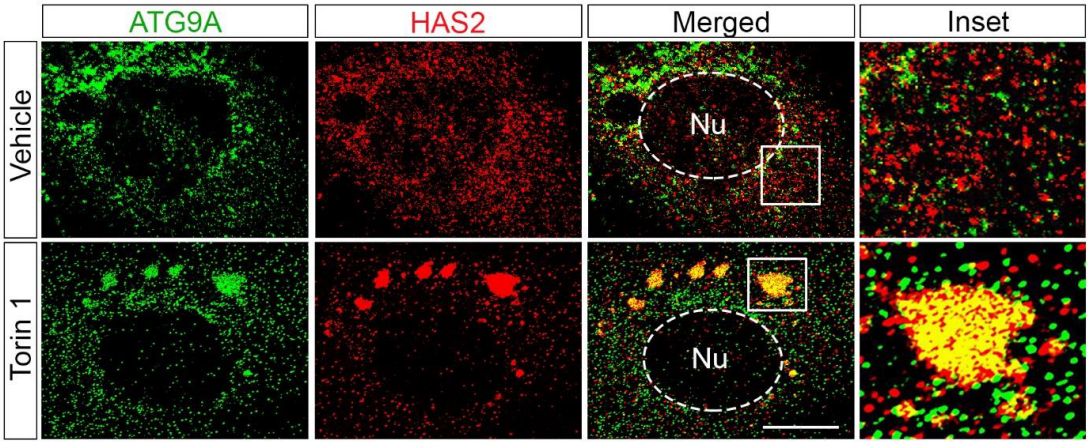
POSITIONS AVAILABLE

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

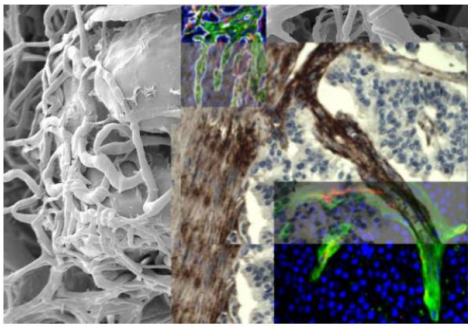


Autophagic induction of HAS2. *Representative super-resolution microscopy images of HUVEC treated with vehicle or Torin 1 (20 nM) for 4 h and immuno-labeled for ATG9A (green) and HAS2 (red). Nucleus (Nu) outlined in white dotted lines. Scale bar, 10 mm.*

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-1α 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 β-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 Research Position available

To determine the molecular and functional characteristics of Tenascin-C matrix niches during tumor immune evolution



One postdoc position (36 months) is available in the **Tumor Microenvironment group** of **Gertraud Orend** (INSERM U1109, Strasbourg) to investigate the tumor microenvironment at cellular and molecular level. The Orend laboratory (https://orend-tme-group.com) is specialized in the analysis of the tumor microenvironment with particular emphasis on the extracellular matrix molecule tenascin-C (Midwood et al., 2016, ***J Cell Sci***) in tumor angiogenesis (Saupe et al., 2013, ***Cell Reports***, Rupp et al., 2016, ***Cell Reports***), metastasis (Sun et al., 2018, ***Cancer Res***, Sun et al., 2019, ***Matrix Bio***) and tumor immunity (Deligne et al., 2020, ***Cancer Immun Res.***, Spenle et al., 2020, ***Cancer Immun Res***).

We offer: a highly dynamic and supportive group of colleagues including researchers, postdocs, PhD and master students and technical personnel with expertise in extracellular matrix research, murine tumor models and tumor immunity. The salary remuneration follows INSERM guidelines taking into account previous experience.

We search: a highly motivated scientist with background in tumor biology, mouse tumor models, immunology, cell culture and biochemistry, high team spirit and good English communication skills. The candidate will map the tenascin-C regulated matrix-immune landscape in its temporal and spatial context in an interdisciplinary consortium of 6 experts in cell and cancer biology, proteomics, transcriptomics, genomics, molecular interactomics analysis and cancer pathology. The aim of this project is to generate novel diagnostic and therapeutic tools to improve cancer treatment.

Interested candidates are invited to send their CV together with a motivation letter and the names of three referees to **Gertraud Orend** (gertraud.orend@inserm.fr).

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)

Effective imaging of cell-matrix adhesions through Electrochemiluminescence (ECL) microscopy

Description: Focal adhesions consist of a complex of cytoskeletal proteins that anchor the cell body to its surrounding matrix. As such, understanding how adhesions interface with their surrounding matrix is critical to deepening our understanding of both matrix biology and cell migration [1]. Imaging focal adhesions in cells on 2D glass using confocal microscopy is relatively painless and allows for stark visualization of focal adhesions that can be easily quantified (see Fig 1a). However, imaging focal adhesions in cells on top of matrices can be very challenging through traditional fluorescence microscopy-based techniques as there can be an overwhelming amount of background noise (see Fig 2a). Since most popular methods to image focal adhesions rely on fluorescence microscopy [2], overcoming the issue of cellular background noise is hard to do. Recently, the use of Electrochemiluminescence (ECL) microscopy has emerged as a powerful tool to image cell-matrix adhesions with minimal background noise [3]. ECL relies on the emission of light from a high-energy electron transfer between two species; therefore, this technique does not require a light source like fluorescence imaging techniques do [4]. Thus, ECL has been shown to substantially eliminate cellular background noise, which is a highly desirable quality when imaging focal adhesions.
Recently, ECL has been specifically modified to image cell-matrix adhesions. In order to induce adhesion formation, a tin oxide electrode is coated with a silica nanochannel membrane. Here, the ECL reaction produces free-flowing luminescence, however there is a stark contrast at the places where the cell interfaces with the membrane. Thus, cell adhesions can be visualized in stark contrast to the cell body [3].

Useful for: Imaging cell-matrix focal adhesions with low background noise, allowing for easy quantification of adhesions.

Challenges/Tips: This is a very specialized technique that requires the use of a transmission electron microscope, which could be a hindrance to this technique being widely used. In addition, this technique cannot be used to visualize focal adhesions in cells within 3D matrices.

1

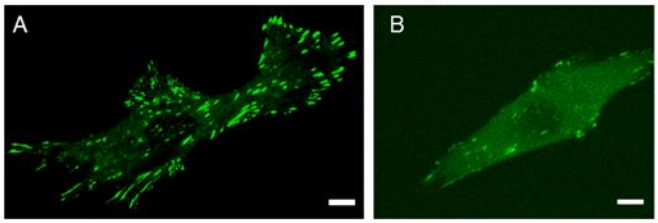
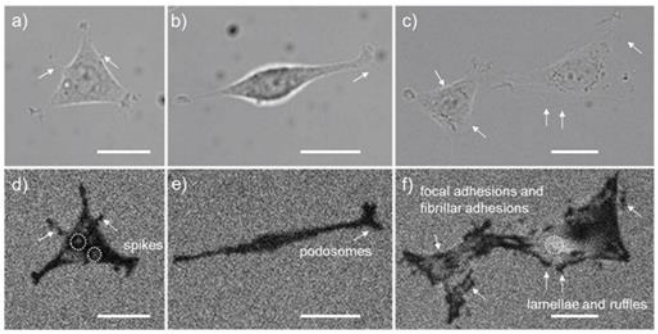


Fig 1. (A) A human foreskin fibroblast (HFF) on 2D glass imaged for Paxillin, a focal adhesion marker, through confocal microscopy. (B) An HFF on top of cell-derived matrix transfected with GFP-Paxillin and imaged through spinning disk confocal microscopy. Scale bar = 10 µm.

2



Source: H. Ding, W. Guo, B. Su, Angew. Chem. Int. Ed. 2020, 59, 449.These are brightfield images (a-c) of PC12 cells compared to ECL images (d-f). In image f, sharp contrast through ECL imaging highlights the focal adhesions in the periphery of the cell. Scale bar = 20 µm.

Sources:

[1] Burridge K. Focal adhesions: a personal perspective on a half century of progress. FEBS J. 2017 Oct;284(20):3355-3361. doi: 10.1111/febs.14195. Epub 2017 Aug 30. PMID: 28796323; PMCID: PMC5643231.

[2] Worth DC, Parsons M. Advances in imaging cell-matrix adhesions. J Cell Sci. 2010 Nov 1;123(Pt 21):3629-38. doi: 10.1242/jcs.064485. PMID: 20971702.

[3] Ding H, Guo W, Su B. Imaging Cell-Matrix Adhesions and Collective Migration of Living Cells by Electrochemiluminescence Microscopy. Angew Chem Int Ed Engl. 2020 Jan 2;59(1):449-456. doi: 10.1002/anie.201911190. Epub 2019 Nov 19. PMID: 31631465.

[4] Liu G, Ma C, Jin BK, Chen Z, Zhu JJ. Direct Electrochemiluminescence Imaging of a Single Cell on a Chitosan Film Modified Electrode. Anal Chem. 2018 Apr 3;90(7):4801-4806. doi: 10.1021/acs.analchem.8b00194. Epub 2018 Mar 13. PMID: 29506381.

Into uncharted territory: exploring the topology of the extracellular matrix

Alejandro Guiliani-Mayorca and Raphael Reuten

We all know how fascinating and complex the extracellular matrix (ECM) is and that the existence of multicellular organisms without the structural ECM would not be possible. The ECM is constantly replaced and remodeled not only during development and throughout life but also during pathological events such as cancer. We strongly feel that we have to understand all levels of the ECM puzzle by means studying single ECM protein activity, ECM composition of organs, and ECM localization and arrangement. All these features will take us closer to understand the ECM and its impact on cell behavior. We would like to present here one puzzle piece, which will complement

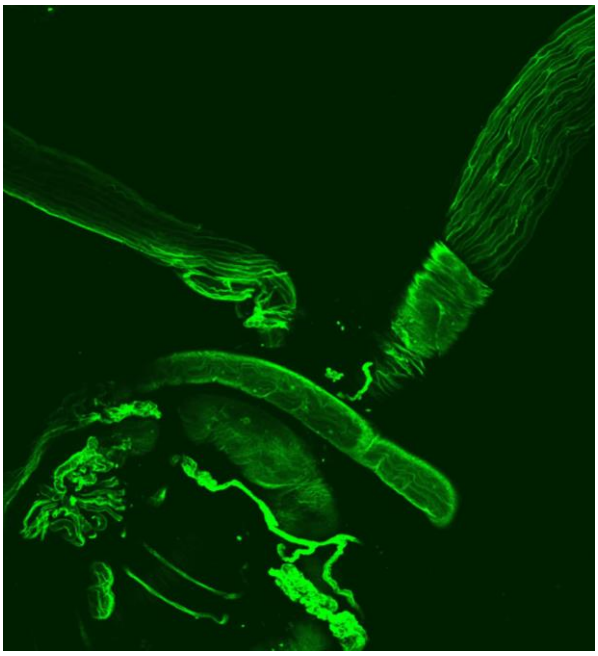


Fig 1. Whole mount ISDoT mammary fat pad stained for collagen type IV. The image depicts peripheral nerve tracks and associated vasculature.

our journey to understand the ECM. This method package might help us to identify the exact localization of ECM proteins and their arrangement in space and time.

Postdoctoral fellow Dr. Alejandro Guiliani-Mayorca in the Erler lab thought about the possibility to visualize the ECM of primary tumors and metastasis and the respective surrounding area in an unprecedented manner. Here, he developed a method, which enables deeper and much more precise imaging of the ECM. Alejandro has thereby pioneered a perfusion-based decellularization method to enhance the study of ECM composition and structure. This method was defined as *in situ* decellularization of tissues (ISDoT)[1]. Alejandro will give us a brief insight into how the idea to decellularize tumor tissues evolved. Alejandro says: "During the winter of 2012-2013 I started transplanting tumors in animals, trying to see whether the site of their emergence influenced their aggression. As results seeped in, cells started to lose their importance, while the structure enveloping them, their "shell", became more relevant for me. I wondered, what is that shell? Does it change, according to site? Is it possible to disassemble a tumor into its components and thus isolate them? At that point I thought that obtaining a tumor ECM was routine; it turned out it wasn't. Unlike organs, tumors lack anatomical vasculature and it would be impossible to catheterize such small vessels in a mouse. During my oral surgery residence, I went through microsurgery training, and this came to my rescue. Here, I hypothesize that a tumor could be decellularized if I catheterize the aorta and not the tumor and additionally clamping all other arteries except the one feeding the tumor."

Thus, his approach is based on vascular-flow-directed decellularization, which allows to deliver decellularization reagents through the cardiovascular system. These decellularization reagents can thereby be delivered to any organ of interest. Moreover, the use of a peristaltic pump guarantees controlled flow rates, which prevents the collapse of the vascular system. In the original publication Alejandro together with Dr. Chris Madsen and Dr. Thomas Cox imaged single ECM proteins in combination with fibrillar collagens using second harmonic generation (SHG). This fascinating method presents a major advance to visualize the 3D structure of the ECM not only within and surrounding tumor tissues but also of all organs. This study to our knowledge remarkably revealed the first characterization of ECM remodeling during both primary tumor progression and at distant metastatic sites. Postdoctoral student Dr. Raphael Reuten joined the Erler lab at the time, in which the ISDoT study was accepted in Nature Medicine. Alejandro and Raphael discussed the need to present the ISDoT method in a precise manner to enable other scientists to perform the sophisticated operation. Our aim was to bring the ISDoT method to the next level and to enable the scientific community to perform this method. Therefore, Alejandro developed additional operations to deliver decellularization reagents to every mouse tissue. Additionally, he designed a precise guide to navigate scientists to choose the right operation, which is needed to decellularize the organ of interest. We further aimed to collect validated antibodies specifically detecting single

ECM proteins. Here, we profoundly profited from the ECM community, which provided several self-made antibodies. In our protocol we present 8 detailed operations to decellularize 33 different mouse tissues and 44 antibodies detecting 35 distinct ECM proteins[2]. At this point we would like to thank all involved scientists and the entire community. We strongly feel that this protocol shapes the basis to start mapping ECM protein localization and arrangement during development, pathological situations, and in ECM protein knockout mice. Moreover, we hypothesize that not only the abundance of ECM proteins plays a significant role in determining cell behavior but also their spatiotemporal arrangement. Thus, we suggest that we should combine the information of biochemical properties of single ECM proteins with their structural appearance in the future. Here, we hope that the ECM community will benefit from our decellularization technique and the validated antibody catalogue, which includes antibodies placed in the RRID depository (https://www.rrids.org). Hence, we believe that our protocol will help to understand the complex and intriguing ECM in a way, which has so far not been possible. Finally, we want to appeal the ECM community for providing antibodies, which have not been included in our protocol[2]. In case you want to perform decellularization of tissues you are interested in studying and/or staining of your ECM protein of interest, please feel free to contact us (alejandro.mayorca@bric.ku.dk and raphael.reuten@bric.ku.dk).

References

1 Mayorca-Guiliani, A. E. *et al.* ISDoT: in situ decellularization of tissues for high-resolution imaging and proteomic analysis of native extracellular matrix. *Nat Med* **23**, 890-898, doi:10.1038/nm.4352 (2017).

2 Mayorca-Guiliani, A. E. *et al.* Decellularization and antibody staining of mouse tissues to map native extracellular matrix structures in 3D. *Nat Protoc*, doi:10.1038/s41596-019-0225-8 (2019).

SPECIAL ISSUES ON THE EXTRACELLULAR MATRIX

Special Issue "Novel Approaches for Targeting Metalloproteinases"

A special issue of Pharmaceuticals (ISSN 1424-8247). This special issue belongs to the section "Biopharmaceuticals".

Deadline for manuscript submissions: 30 November 2020.
https://www.mdpi.com/journal/pharmaceuticals/special_issues/Targeting_Metalloproteinases

Guest Editor Dr. Salvatore Santamaria

Department of Immunology and Inflammation, Imperial College London, Centre for Haematology, 5th Floor Commonwealth Building, Hammersmith Hospital Campus, Du Cane Road, London, W12 0NN, UK

Interests: ADAMTS; proteoglycans; monoclonal antibodies; exosite inhibitors; enzyme kinetics; proteomics; proteoglycanomics; phage display

Dear Colleagues,

Metalloproteinases play key roles in physiological processes such as embryonic development, wound healing, angiogenesis, and blood coagulation, as well as pathologies like arthritis, cardiovascular disease, and cancer. In the therapeutic context, either decreasing or increasing the activity of a particular metalloproteinase may be ideal. This can be achieved, for example, through the action of molecules able to bind to substrate-binding sites (exosites) present on the ancillary domains of these enzymes or interfere with their transcriptional or post-translational regulation.

Potential contributors are invited to submit papers concerning modulators of metalloproteinase activity in any pharmaceutical or related context. Particularly welcome are studies involving exosite inhibitors/enhancers, substrate mimetics, natural products, and glycoconjugates, as well as peptides, aptamers, monoclonal antibodies, and engineered proteins. Novel approaches for the therapeutic delivery of these reagents are also appreciated.

I look forward to reading your submission.

Dr. Salvatore Santamaria
Guest Editor
s.santamaria@imperial.ac.uk

Frontiers Research Topics

ADAM, ADAMTS and Astacin Proteases: Challenges and Breakthroughs in the -Omics Era
https://www.frontiersin.org/research-topics/14533/adam-adamts-and-astacin-proteases-challenges-and-breakthroughs-in-the--omics-era

Submission Deadlines
29 September 2020 Abstract
30 March 2021 Manuscript

Topic Editors
Salvatore Santamaria
Hang Fai Kwok
Kazuhiro Yamamoto
Simone Dario Scilabra
Rens de Groot

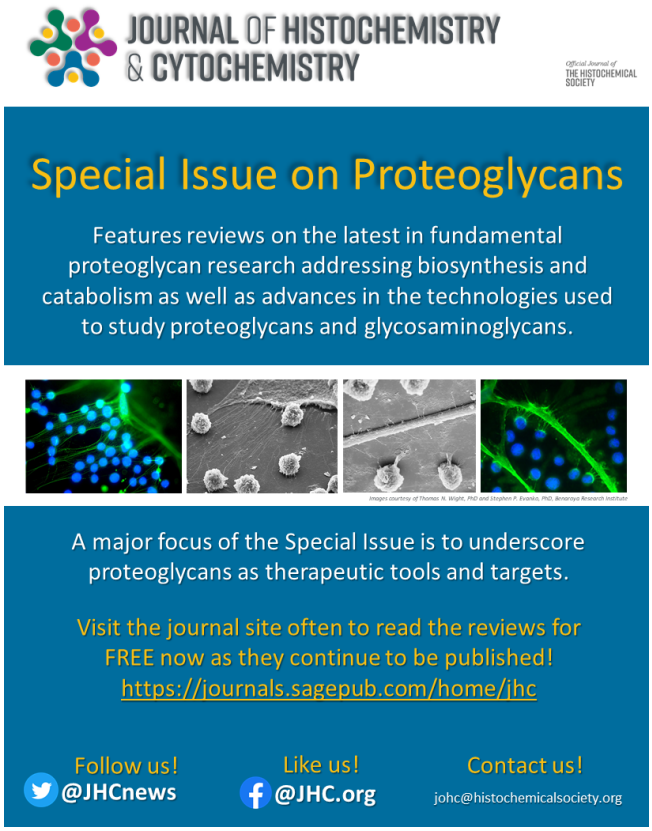
SPECIAL ISSUE ON PROTEOGLYCANS

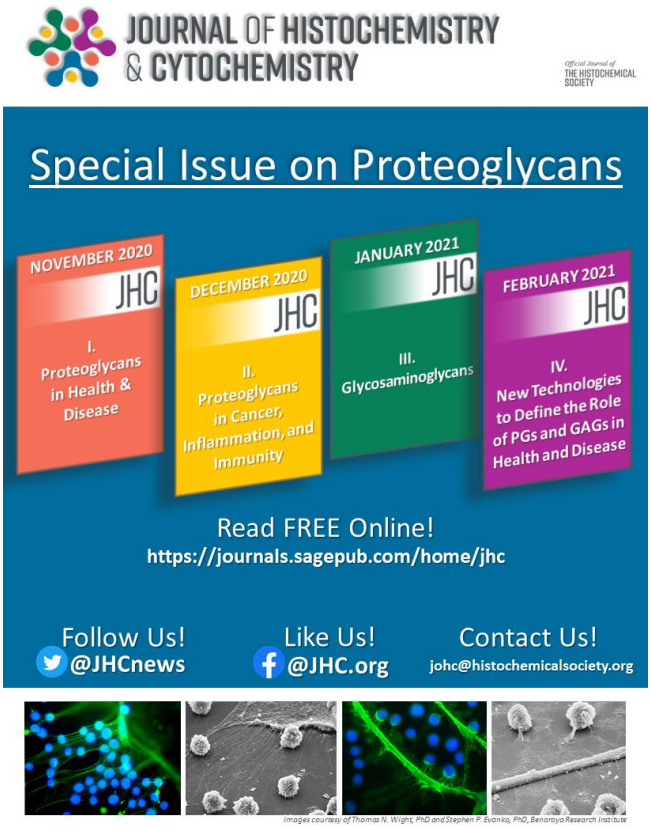
Journal of Histochemistry and Cytochemistry

Editor: Liliana Schaeffer

All published special issue papers will be hosted here and will be permanently freely available: https://journals.sagepub.com/topic/collections-jhc/jhc-1-special_issue_on_proteoglycans/jhc?pbEditor=true.

The Special Issue is also being prominently featured via a carousel slide on the main page of the JHC website at https://journals.sagepub.com/home/jhc.





International Journal of *Molecular Sciences*

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Matricellular Proteins: Modifiers of Cell Behavior in Development, Disease & Tissue Remodeling

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Deadline for manuscript submissions:
15 February 2021

Message from the Guest Editors

Dear Colleagues,

Matricellular proteins were first described by the Bornstein group in 1995. Since then, they have become a major focus of research in the area of extracellular matrix and cell biology. As a class of matrix proteins, matricellular proteins are characterized by their ability to modify the cell phenotype in health and disease and have been implicated in numerous cancer types, acute healing, and fibrosis. Matricellular proteins are important during development, but are typically restricted to tissue remodeling, wound repair, and remodeling in the normal adult.

Matricellular proteins interact with cell surface receptors, such as integrins, and are able to bind growth factors as well as the structural components of the matrix, such as collagen. Galectins, tenascins, thrombospondins, SPARC, osteopontin, hevin, periostin, and bone sialoprotein are all classed as matricellular proteins, each with varying functions. It appears that matricellular proteins are essential to the tissue response to pathological insults.

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Special Issue

International Journal of *Molecular Sciences*

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Extracellular Matrix Aging, Principles and Consequences

Guest Editor:

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Deadline for manuscript submissions:
31 May 2021

Message from the Guest Editor

The extracellular matrix is a complex 3D network providing support, mechanical input, and biochemical signals to cells. Numerous studies have underlined the fact that the matrix is essential for proper tissue functioning and maintenance. During the aging process, the extracellular matrix is altered, modified, and sometimes degraded, resulting in local molecular changes that define new information for the surrounding cells that change their behavior to adapt to this new situation. This is notably relevant for matrix fibrous proteins, which can accumulate alterations, eventually resulting in functional failure with pathological consequences.

This Special Issue will consider research articles and reviews about the processes leading to extracellular matrix ageing and its consequences at the molecular, cellular, tissular, or physiological levels.

mdpi.com/si/61848

Special Issue

TENASCINS: KEY PLAYERS IN TISSUE HOMEOSTASIS AND DEFENSE

Tenascin-C, -R, -X and –W are four members of a family of large, multimodular extracellular matrix molecules. By virtue of a large repertoire of binding partners, including other matrix molecules, soluble factors, and cell surface receptors, tenascins are key regulators of both tissue architecture and cell phenotype.

Each family member exhibits a specifically restricted, non-overlapping, pattern of expression that is tightly controlled in healthy tissues, helping to create distinct microenvironmental niches that program localized cell behavior, for example in stem cell niches, in areas of high mechanical load, in connective tissue and in the perineural nets. The expression of these molecules is transiently upregulated in response to cellular stress and tissue injury, where they each play diverse roles in activating immune responses designed to restore homeostasis. However, misregulated expression of these molecules is associated with aberrant inflammation in inflammatory, fibrotic, and metabolic diseases, and cancer.

This Research Topic aims to look back over the discovery of these matrix molecules nearly 40 years ago and highlight how our understanding of tenascin-related biology, and pathology, has exponentially progressed over the last few years. We also address how these molecules are being exploited for use in the diagnosis and treatment of inflammatory and fibrotic diseases and cancer, in the context of immune checkpoint therapy and beyond. We welcome authors to submit Original Research and Review articles focusing on:

1. New emerging roles for tenascins in inflammation, infection and tissue repair
2. Tenascins contribution to pathological inflammation in diseases including of the brain, gut, kidney, cardiovascular and musculoskeletal systems
3. Novel approaches for studying and targeting tenascin-mediated inflammation
4. Tenascins in tumor immunosurveillance
5. The interplay between tenascins and immune checkpoint therapies

Keywords: extracellular matrix, tissue microenvironment, tenascins, inflammation, autoimmune disease, tumor immunology, checkpoint inhibition

Editors: Kim Midwood (University of Oxford, UK), Gertraud Orend (Strasbourg, France), Kyoko Imanaka-Yoshida (Mie University, Tsu, Japan)

Contributions are still welcome because the submission deadline has been extended until end of October 2020.

RECENT PAPERS

Lockhart-Cairns MP, Newandee H, Thomson J, Weiss AS, Baldock C, Tarakanova A. **Transglutaminase-Mediated Cross-Linking of Tropoelastin to Fibrillin Stabilises the Elastin Precursor Prior to Elastic Fibre Assembly**. J Mol Biol. 2020 doi: 10.1016/j.jmb.2020.08.023.

Corresponding authors: clair.baldock@manchester.ac.uk, anna.tarakanova@uconn.edu

Abstract: *Elastic fibres are essential components of all mammalian elastic tissues such as blood vessels, lung and skin, and are critically important for the mechanical properties they endow. The main components of elastic fibres are elastin and fibrillin, where correct formation of elastic fibres requires a fibrillin microfibril scaffold for the deposition of elastin. It has been demonstrated previously that the interaction between fibrillin and tropoelastin, the elastin precursor, increases the rate of assembly of tropoelastin. Furthermore, tropoelastin and fibrillin can be cross-linked by transglutaminase-2 but the function of cross-linking on their elastic properties is yet to be elucidated. Here we show that transglutaminase cross-linking supports formation of a 1:1 stoichiometric fibrillin-tropoelastin complex. SAXS data show that the complex retains features of the individual proteins, but is elongated supporting end-to-end assembly. Elastic network models were constructed to compare the dynamics of tropoelastin and fibrillin individually as well as in the cross-linked complex. Normal mode analysis was performed to determine the structures' most energetically favourable, biologically accessible motions which show that within the complex, tropoelastin is less mobile and this molecular stabilisation extends along the length of the tropoelastin molecule to regions remote from the cross-linking site. Together, these data suggest a long-range stabilising effect of cross-linking that occurs due to the covalent linkage of fibrillin to tropoelastin. This work provides insight into the interactions of tropoelastin and fibrillin and how cross-link formation stabilises the elastin precursor so it is primed for elastic fibre assembly*.

Peeters S, Decramer A, Cain SA, Houpt P, Verstreken F, Noyez J, Hermans C, Jacobs W, Lammens M, Fransen E, Kumar AA, Vandeweyer G, Loeys B, Van Hul W, Baldock C, Boudin E, Mortier G. **Delineation of a new fibrillino-2-pathy with evidence for a role of FBN2 in the pathogenesis of carpal tunnel syndrome**. J Med Genet. 2020 doi:10.1136/jmedgenet-2020-107085.

Corresponding author: geert.mortier@uantwerpen.be

Abstract: *Background: Although carpal tunnel syndrome (CTS) is the most common form of peripheral entrapment neuropathy, its pathogenesis remains largely unknown. An estimated heritability index of 0.46 and an increased familial occurrence indicate that genetic factors must play a role in the pathogenesis. Methods and results: We report on a family in which CTS occurred in subsequent generations at an unusually young age. Additional clinical features included brachydactyly and short Achilles tendons resulting in toe walking in childhood. Using exome sequencing, we identified a heterozygous variant (c.5009T>G; p.Phe1670Cys) in the fibrillin-2 (FBN2) gene that co-segregated with the phenotype in the family. Functional assays showed that the missense variant impaired integrin-mediated cell adhesion and migration. Moreover, we observed an increased transforming growth factor-β signalling and fibrosis in the carpal tissues of affected individuals. A variant burden test in a large cohort of patients with CTS revealed a significantly increased frequency of rare (6.7% vs 2.5%-3.4%, p<0.001) and high-impact (6.9% vs 2.7%, p<0.001) FBN2 variants in patient alleles compared with controls. Conclusion: The identification of a novel FBN2 variant (p.Phe1670Cys) in a unique family with early onset CTS, together with the observed increased frequency of rare and high-impact FBN2 variants in patients with sporadic CTS, strongly suggest a role of FBN2 in the pathogenesis of CTS.*

Nandadasa S, Szafron JM, Pathak V, Murtada SI, Kraft CM, O'Donnell A, Norvik C, Hughes C, Caterson B, Domowicz MS, Schwartz NB, Tran-Lundmark K, Veigl M, Sedwick D, Philipson EH, Humphrey JD, Apte SS. **Vascular dimorphism**

ensured by regulated proteoglycan dynamics favors rapid umbilical artery closure at birth. Elife. 2020 Sep 10;9:e60683. doi: 10.7554/eLife.60683. Online ahead of print.PMID: 32909945
Corresponding author: aptes@ccf.org
Abstract: *The umbilical artery lumen closes rapidly at birth, preventing neonatal blood loss, whereas the umbilical vein remains patent longer. Here, analysis of umbilical cords from humans and other mammals identified differential arterial-venous proteoglycan dynamics as a determinant of these contrasting vascular responses. The umbilical artery, but not the vein, has an inner layer enriched in the hydrated proteoglycan aggrecan, external to which lie contraction-primed smooth muscle cells (SMC). At birth, SMC contraction drives inner layer buckling and centripetal displacement to occlude the arterial lumen, a mechanism revealed by biomechanical observations and confirmed by computational analyses. This vascular dimorphism arises from spatially regulated proteoglycan expression and breakdown. Mice lacking aggrecan or the metalloprotease ADAMTS1, which degrades proteoglycans, demonstrate their opposing roles in umbilical vascular dimorphism, including effects on SMC differentiation. Umbilical vessel dimorphism is conserved in mammals, suggesting that differential proteoglycan dynamics and inner layer buckling were positively selected during evolution.*

Martin DR, Witten JC, Tan CD, Rodriguez ER, Blackstone EH, Pettersson GB, Seifert DE, Willard BB, Apte SS. **Proteomics identifies a convergent innate response to infective endocarditis and extensive proteolysis in vegetation components.** JCI Insight. 2020 Jul 23;5(14):e135317. doi: 10.1172/jci.insight.135317.
Corresponding author: aptes@ccf.org
Abstract: *Infective endocarditis is a life-threatening infection of heart valves and adjacent structures characterized by vegetations on valves and other endocardial surfaces, with tissue destruction and risk of embolization. We used high-resolution mass spectrometry to define the proteome of staphylococcal and non-staphylococcal vegetations and Terminal Amine Isotopic Labeling of Substrates (TAILS) to define their proteolytic landscapes. These approaches identified over 2000 human proteins in staphylococcal and non-staphylococcal vegetations. Individual vegetation proteomes demonstrated comparable profiles of quantitatively major constituents that overlapped with serum, platelet, and neutrophil proteomes. Staphylococcal vegetation proteomes resembled one another more than the proteomes of non-staphylococcal vegetations. TAILS demonstrated extensive proteolysis within vegetations, with numerous previously undescribed cleavages. Several proteases and pathogen-specific proteins, including virulence factors, were identified in most vegetations. Proteolytic peptides in fibronectin and complement C3 were identified as potential infective endocarditis biomarkers. Overlap of staphylococcal and non-staphylococcal vegetation proteomes suggests a convergent thrombotic and immune response to endocardial infection by diverse pathogens. However, the differences between staphylococcal and non-staphylococcal vegetations and internal variance within the non-staphylococcal group indicate that additional pathogen- or patient-specific effects exist. Pervasive proteolysis of vegetation components may arise from vegetation-intrinsic proteases and destabilize vegetations, contributing to embolism.*

Koch CD, Lee CM, Apte SS. Review: **Aggrecan in Cardiovascular Development and Disease**. J Histochem Cytochem. 2020 Sep 1:22155420952902. doi: 10.1369/0022155420952902. Online ahead of print
Corresponding author: aptes@ccf.org
Abstract: *Aggrecan is a large proteoglycan that forms giant hydrated aggregates with hyaluronan in the extracellular matrix (ECM). The extraordinary resistance of these aggregates to compression explains their abundance in articular cartilage of joints where they ensure adequate load-bearing. In the brain, they provide mechanical buffering and contribute to formation of perineuronal nets, which regulate synaptic plasticity. Aggrecan is also present in cardiac jelly, developing heart valves, and blood vessels during cardiovascular development. Whereas aggrecan is essential for skeletal development, its function in the developing cardiovascular system remains to be fully elucidated. An excess of aggrecan was demonstrated in cardiovascular tissues in aortic*

aneurysms, atherosclerosis, vascular re-stenosis after injury, and varicose veins. It is a product of vascular smooth muscle and is likely to be an important component of pericellular matrix, where its levels are regulated by proteases. Aggrecan can contribute to specific biophysical and regulatory properties of cardiovascular ECM via the diverse interactions of its domains, and its accumulation is likely to have a significant role in developmental and disease pathways. Here, the established biological functions of aggrecan, its cardiovascular associations, and potential roles in cardiovascular development and disease are discussed.

Vallet SD, Clerc O, Ricard-Blum S. **Glycosaminoglycan-Protein Interactions: The First Draft of the Glycosaminoglycan Interactome**. J Histochem Cytochem 2020 Aug 6;22155420946403. doi: 10.1369/0022155420946403. Online ahead of print.
Corresponding author: sylvie.ricard-blum@univ-lyon1.fr
Abstract: *The six mammalian glycosaminoglycans (GAGs), chondroitin sulfate, dermatan sulfate, heparin, heparan sulfate, hyaluronan, and keratan sulfate, are linear polysaccharides. Except for hyaluronan, they are sulfated to various extent, and covalently attached to proteins to form proteoglycans. GAGs interact with growth factors, morphogens, chemokines, extracellular matrix proteins and their bioactive fragments, receptors, lipoproteins, and pathogens. These interactions mediate their functions, from embryonic development to extracellular matrix assembly and regulation of cell signaling in various physiological and pathological contexts such as angiogenesis, cancer, neurodegenerative diseases, and infections. We give an overview of GAG–protein interactions (i.e., specificity and chemical features of GAG- and protein-binding sequences), and review the available GAG–protein interaction networks. We also provide the first comprehensive draft of the GAG interactome composed of 832 biomolecules (827 proteins and five GAGs) and 932 protein–GAG interactions. This network is a scaffold, which in the future should integrate structures of GAG–protein complexes, quantitative data of the abundance of GAGs in tissues to build tissue-specific interactomes, and GAG interactions with metal ions such as calcium, which plays a major role in the assembly of the extracellular matrix and its interactions with cells. This contextualized interactome will be useful to identify druggable GAG–protein interactions for therapeutic purpose.*

Cangkrama M, Wietecha M, Werner S. **Wound Repair, Scar Formation, and Cancer: Converging on Activin**. Trends Mol Med. 2020 Aug 30:S1471-4914(20)30188-X. doi: 10.1016/j.molmed.2020.07.009. Online ahead of print. PMID: 32878730 Review.
Corresponding author: sabine.werner@biol.ethz.ch
Abstract: *Wound repair is a highly regulated process that requires the interaction of various cell types. It has been shown that cancers use the mechanisms of wound healing to promote their own growth. Therefore, it is of importance to identify common regulators of wound repair and tumor formation and to unravel their functions and mechanisms of action. An exciting example is activin, which acts on multiple cell types in wounds and tumors, thereby promoting healing, but also scar formation and tumorigenesis. Here, we summarize current knowledge on the role of activin in these processes and highlight the therapeutic potential of activin or activin antagonists for the treatment of impaired healing or excessive scarring and cancer, respectively.*

Ben-Yehuda Greenwald M, Tacconi C, Jukic M, Joshi N, Hiebert P, Brinckmann J, Tenor H, Naef R, Werner S. **A Dual-Acting Nitric Oxide Donor and Phosphodiesterase 5 Inhibitor Promotes Wound Healing in Normal Mice and Mice with Diabetes**. J Invest Dermatol. 2020 Jun 27:S0022-202X(20)31725-5. doi: 10.1016/j.jid.2020.05.111. Online ahead of print. PMID: 32598925
Corresponding author: sabine.werner@biol.ethz.ch
Abstract: *Chronic wounds affect a large percentage of the population worldwide and cause significant morbidity. Unfortunately, efficient compounds for the treatment of chronic wounds are yet not available. Endothelial*

dysfunction, which is at least in part a result of compromised nitric oxide production and concomitant reduction in cGMP levels, is a major pathologic feature of chronic wounds. Therefore, we designed and synthesized a compound with a unique dual-acting activity (TOP-N53), acting as a nitric oxide donor and phosphodiesterase 5 inhibitor, and applied it locally to full-thickness skin wounds in healthy and healing-impaired mice with diabetes. TOP-N53 promoted keratinocyte proliferation, angiogenesis, and collagen maturation in healthy mice without accelerating the wound inflammatory response or scar formation. Most importantly, it partially rescued the healing impairment of mice with genetically determined type II diabetes (db/db) by stimulating re-epithelialization and granulation tissue formation, including angiogenesis. In vitro studies with human and murine primary cells showed a positive effect of TOP-N53 on keratinocyte and fibroblast migration, keratinocyte proliferation, and endothelial cell migration and tube formation. These results demonstrate a remarkable healing-promoting activity of TOP-N53 by targeting the major resident cells in the wound tissue.

Jamie Fitzgerald. **Applications of CRISPR for musculoskeletal research.** Bone Joint Res 2020;9(7):351–359
Corresponding author: jfitzge2@hfhs.org
Abstract: *The ability to edit DNA at the nucleotide level using clustered regularly interspaced short palindromic repeats (CRISPR) systems is a relatively new investigative tool that is revolutionizing the analysis of many aspects of human health and disease, including orthopaedic disease. CRISPR, adapted for mammalian cell genome editing from a bacterial defense system, has been shown to be a flexible, programmable, scalable, and easy-to-use gene editing tool. Recent improvements increase the functionality of CRISPR through the engineering of specific elements of CRISPR systems, the discovery of new, naturally occurring CRISPR molecules, and modifications that take CRISPR beyond gene editing to the regulation of gene transcription and the manipulation of RNA. Here, the basics of CRISPR genome editing will be reviewed, including a description of how it has transformed some aspects of molecular musculoskeletal research, and will conclude by speculating what the future holds for the use of CRISPR-related treatments and therapies in clinical orthopaedic practice.*

Fitzgerald J, Feist C., Dietz P., Moore S., and Basel D. **A Deep Intronic Variant Activates a Pseudoexon in the MTM1Gene in a Family with X-Linked Myotubular Myopathy.** Mol Syndromol. doi.org/10.1159/000510286
Corresponding author: jfitzge2@hfhs.org
Abstract: *We report a novel intronic variant in the MTM1 gene in 4 males in a family with severe X-linked myotubular myopathy. The A>G variant in deep intronic space activates a cryptic 5' donor splice site resulting in the inclusion of a 48-bp pseudoexon into the mature MTM1 mRNA. The variant is present in all affected males, absent in unaffected males, and heterozygous in the mother of the affected males. The included intronic sequence contains a premature stop codon, and experiments using a translational inhibitor indicate that the mutant mRNAs undergo nonsense-mediated decay. We conclude that affected males produce no, or low, levels of MTM1 mRNA likely leading to a significant reduction of myotubularin-1 protein resulting in the severe neonatal myopathy present in this family. The study highlights the need to consider noncoding variants in genomic screening in families with X-linked myotubular myopathy.*

Abety AN, Pach E, Giebeler N, Fromme JE, Aramadhaka LR, Mauch C, Fox JW, Zigrino P. Loss of ADAM9 Leads to Modifications of the Extracellular Matrix Modulating Tumor Growth. Biomolecules. 2020 Sep 7;10(9):E1290. doi: 10.3390/biom10091290.
Corresponding author: paola.zigrino@uni-koeln.de
Abstract: *ADAM9 is a metalloproteinase strongly expressed at the tumor-stroma border by both tumor and stromal cells. We previously showed that the host deletion of ADAM9 leads to enhanced growth of grafted B16F1 melanoma cells by a mechanism mediated by TIMP1 and the TNF-α/sTNFR1 pathway. This study aimed to dissect the structural modifications in the tumor microenvironment due to the stromal expression of ADAM9 during melanoma*

progression. We performed proteomic analysis of peritumoral areas of ADAM9 deleted mice and identified the altered expression of several matrix proteins. These include decorin, collagen type XIV, fibronectin, and collagen type I. Analysis of these matrices in the matrix producing cells of the dermis, fibroblasts, showed that ADAM9-/- and wild type fibroblasts synthesize and secreted almost comparable amounts of decorin. Conversely, collagen type I expression was moderately, but not significantly, decreased at the transcriptional level, and the protein increased in ADAM9-/- fibroblast mono- and co-cultures with melanoma media. We show here for the first time that ADAM9 can release a collagen fragment. Still, it is not able to degrade collagen type I. However, the deletion of ADAM9 in fibroblasts resulted in reduced MMP-13 and -14 expression that may account for the reduced processing of collagen type I. Altogether, the data show that the ablation of ADAM9 in the host leads to the altered expression of peritumoral extracellular matrix proteins that generate a more favorable environment for melanoma cell growth. These data underscore the suppressive role of stromal expression of ADAM9 in tumor growth and call for a better understanding of how protease activities function in a cellular context for improved targeting.

Adamo CS, Zuk AV, Sengle G**. The fibrillin microfibril/ elastic fiber network: A critical extracellular supramolecular: scaffold to balance skin homeostasis.** Exp Dermatol. 2020 Sep 13. doi: 10.1111/exd.14191. Online ahead of print.
Corresponding author: gsengle@uni-koeln.de
Abstract: *Supramolecular networks composed of fibrillins (fibrillin-1 and -2) and associated ligands form intricate cellular microenvironments which balance skin homeostasis and direct remodeling. Fibrillins assemble into microfibrils which are not only indispensable for conferring and elasticity to the skin, but also control the bioavailability of growth factors targeted to the extracellular matrix architecture. Fibrillin microfibrils (FMF) represent the core scaffolds for elastic fiber formation, but they also decorate the surface of elastic fibers and form independent networks. In normal dermis, elastic fibers are suspended in a three-dimensional basket-like lattice of FMF intersecting basement membranes at the dermal-epidermal junction and thus conferring pliability to the skin. The importance of FMF for skin homeostasis is illustrated by the clinical features caused by mutations in the human fibrillin genes (FBN1, FBN2), summarized as "fibrillinopathies". In skin, fibrillin mutations result in phenotypes ranging from thick, stiff and fibrotic skin to thin, lax and hyperextensible skin. The most plausible explanation for this spectrum of phenotypic outcomes is that FMF regulate growth factor signaling essential for proper growth and homeostasis of the skin. Here, we will give an overview about the current understanding of the underlying pathomechanisms leading to fibrillin-dependent fibrosis as well as forms of cutis laxa caused by mutational inactivation of FMF associated ligands.*

Berberich B, Thriene K, Gretzmeier C, Kühl T, Bayer H, Athanasiou I, Rafei-Shamsabadi DA, Bruckner-Tuderman L, Nyström A, Kiritsi D, Dengjel J. **Proteomic Profiling of Fibroblasts Isolated from Chronic Wounds Identifies Disease-Relevant Signaling Pathways.** J Invest Dermatol. 2020 Apr 17:S0022-202X(20)31376-2. doi: 10.1016/j.jid.2020.02.040.
Corresponding author: joern.dengjel@unifr.ch
Abstract: *Chronic skin wounds accompany many prevalent age-related diseases and are a major cause of morbidity and mortality. Both keratinocytes and fibroblasts contribute to the pathomechanisms in chronic skin wounds. Dysregulated pathways in the epidermis have been extensively studied, but little is known of the influence of dermal fibroblasts on chronic wounding. We isolated fibroblasts from chronic wounds, propagated them in vitro, and analyzed them using proteomic profiling in combination with functional characterization of the proteomic changes. Chronic wound-associated fibroblasts exhibit a unique proteome profile characteristic of lysosomal dysfunction and dysregulated TGFβ signaling. They display a decreased propensity for cell proliferation and migration, combined with an enhanced ability to contract the extracellular matrix. With these properties, chronic wound-associated fibroblasts actively contribute to pathological inabilities to close wounds and represent potential targets for pharmacological interference for changing cellular phenotypes.*

Bornert O, Hogervorst M, Nauroy P, Bischof J, Swildens J, Athanasiou I, Tufa SF, Keene DR, Kiritsi D, Hainzl S, Murauer EM, Marinkovich MP, Platenburg G, Hausser I, Wally V, Ritsema T, Koller U, Haisma EM, Nyström A. **QR-313, an antisense oligonucleotide, shows therapeutic efficacy for treatment of dominant and recessive dystrophic epidermolysis bullosa: a preclinical study**. J Invest Dermatol. 2020 Sep 15:S0022-202X(20)32061-3. doi: 10.1016/j.jid.2020.08.018.

Corresponding author: alexander.nystroem@uniklinik-freiburg.de

Abstract: *Dystrophic epidermolysis bullosa (DEB) is a blistering skin disease caused by mutations in the gene COL7A1 encoding collagen VII. DEB can be inherited in a recessive (RDEB) or dominant (DDEB) manner and is associated with a high wound burden. Perpetual cycles of wounding and healing drive fibrosis in DDEB and RDEB, as well as the formation of a tumor-permissive microenvironment. Prolonging wound free episodes by improving the quality of wound healing would therefore confer substantial benefit for individuals with DEB. The collagenous domain of collagen VII is encoded by 82 in-frame exons, which makes splice-modulation therapies attractive for DEB. Indeed, antisense oligonucleotide (AON)-based exon skipping has shown promise for RDEB. However, the suitability of AONs for treatment of DDEB remains unexplored. Here, we developed QR-313 - a clinically applicable, potent AON specifically targeting exon73. We show the feasibility of topical delivery of QR-313 in a carbomer-composed gel for treatment of wounds to restore collagen VII abundance in human RDEB skin. Importantly, our data reveal that QR-313 also shows direct benefit for DDEB caused by exon73 mutations. Thus, the same topically applied therapeutic could be used to improve the wound healing quality in RDEB and DDEB.*

Brod F, Fässler R. **A FAK conundrum is solved: activation and organization of focal adhesion kinase at the plasma membrane.** EMBO J. 2020 Aug 31:e106234. doi: 10.15252/embj.2020106234.

Corresponding author: faessler@biochem.mpg.de

Abstract: *Focal adhesion kinase (FAK) is a central mediator of cell adhesion, acting both as a scaffold and as catalytically active kinase. Acebrón et al (2020) use cryo-electron microscopy (cryo-EM) to visualize the dramatic structural changes that occur upon FAK recruitment to the plasma membrane, which releases FAK autoinhibition and induces its oligomerization. Since activity control via autoinhibition and protein clustering are features also utilized by other focal adhesion (FA) proteins, they have moved center stage in the endeavor to understand the complex process of cell adhesion regulation.*

Börschel CS, Stejskalova A, Schäfer SD, Kiesel L, Götte M. **miR-142-3p Reduces the Size, Migration, and Contractility of Endometrial and Endometriotic Stromal Cells by Targeting Integrin- and Rho GTPase-Related Pathways That Regulate Cytoskeletal Function.** Biomedicines. 2020 Aug 18;8(8):291. doi: 10.3390/biomedicines8080291.

Corresponding author: mgotte@uni-muenster.de

Abstract: *Downregulated microRNA-142-3p signaling contributes to the pathogenesis of endometriosis, an invasive disease where the lining of the uterus grows at ectopic locations, by yet incompletely understood mechanisms. Using bioinformatics and in vitro assays, this study identifies cytoskeletal regulation and integrin signaling as two relevant categories of miR-142-3p targets. qPCR revealed that miR-142-3p upregulation in St-T1b cells downregulates Rho-associated protein kinase 2 (ROCK2), cofilin 2 (CFL2), Ras-related C3 botulinum toxin substrate 1 (RAC1), neural Wiskott-Aldrich syndrome protein (WASL), and integrin α-V (ITGAV). qPCR and Western-blotting showed miR-142-3p effect on WASL and ITGAV was significant also in primary endometriotic stroma cells. Luciferase reporter assays in ST-T1b cells then confirmed direct regulation of ITGAV and WASL. On the functional side, miR-142-3p upregulation significantly reduced ST-T1b cell size, the size of vinculin plaques, migration through fibronectin-coated transwell filters, and the ability of ST-T1b and primary endometriotic stroma cells to contract collagen I gels. These results suggest that miR-142-3p has a strong mechanoregulatory effect on endometrial*

stroma cells and its external administration reduces the invasive endometrial phenotype. Within the limits of an in vitro investigation, our study provides new mechanistic insights into the pathogenesis of endometriosis and provides a perspective for the development of miR-142-3p based drugs for inhibiting invasive growth of endometriotic cells.

Dengjel J, Bruckner-Tuderman L, Nyström A. **Skin proteomics - analysis of the extracellular matrix in health and disease.** Expert Rev Proteomics. 2020 May;17(5):377-391. doi: 10.1080/14789450.2020.1773261.
Corresponding author: joern.dengjel@unifr.ch, leena.bruckner-tuderman@uniklinik-freiburg.de, alexander.nystroem@uniklinik-freiburg.de
Abstract: *Introduction: The skin protects the human body from external insults and regulates water and temperature homeostasis. A highly developed extracellular matrix (ECM) supports the skin and instructs its cell functions. Reduced functionality of the ECM is often associated with skin diseases that cause physical impairment and also have implications on social interactions and quality of life of affected individuals. Areas covered: With a focus on the skin ECM we discuss how mass spectrometry (MS)-based proteomic approaches first contributed to establishing skin protein inventories and then facilitated elucidation of molecular functions and disease mechanisms. Expert opinion: MS-based proteomic approaches have significantly contributed to our understanding of skin pathophysiology, but also revealed the challenges in assessing the skin ECM. The numerous posttranslational modifications of ECM proteins, like glycosylation, crosslinking, oxidation, and proteolytic maturation in disease settings can be difficult to tackle and remain understudied. Increased ease of handling of LC-MS/MS systems and automated/streamlined data analysis pipelines together with the accompanying increased usage of LC-MS/MS approaches will ensure that in the coming years MS-based proteomic approaches will continue to play a vital part in skin disease research. They will facilitate the elucidation of molecular disease mechanisms and, ultimately, identification of new druggable targets.*

Espinoza-Sánchez NA, Götte M. **Role of cell surface proteoglycans in cancer immunotherapy.** Semin Cancer Biol. 2020 May;62:48-67. doi: 10.1016/j.semcancer.2019.07.012.
Corresponding author: mgotte@uni-muenster.de
Abstract: *Over the past few decades, understanding how tumor cells evade the immune system and their communication with their tumor microenvironment, has been the subject of intense investigation, with the aim of developing new cancer immunotherapies. The current therapies against cancer such as monoclonal antibodies against checkpoint inhibitors, adoptive T-cell transfer, cytokines, vaccines, and oncolytic viruses have managed to improve the clinical outcome of the patients. However, in some tumor entities, the response is limited and could benefit from the identification of novel therapeutic targets. It is known that tumor-extracellular matrix interplay and matrix remodeling are necessary for anti-tumor and pro-tumoral immune responses. Proteoglycans are dominant components of the extracellular matrix and are a highly heterogeneous group of proteins characterized by the covalent attachment of a specific linear carbohydrate chain of the glycosaminoglycan type. At cell surfaces, these molecules modulate the expression and activity of cytokines, chemokines, growth factors, adhesion molecules, and function as signaling co-receptors. By these mechanisms, proteoglycans influence the behavior of cancer cells and their microenvironment during the progression of solid tumors and hematopoietic malignancies. In this review, we discuss why cell surface proteoglycans are attractive pharmacological targets in cancer, and we present current and recent developments in cancer immunology and immunotherapy utilizing proteoglycan-targeted strategies.*

Etich J, Rehberg M, Eckes B, Sengle G, Semler O, Zaucke F. **Signaling pathways affected by mutations causing osteogenesis imperfecta.** Cell Signal. 2020 Sep 24:109789. doi: 10.1016/j.cellsig.2020.109789.
Corresponding author: julia.etich@kgu.de

Abstract: *Osteogenesis imperfecta (OI) is a clinically and genetically heterogeneous connective tissue disorder characterized by bone fragility and skeletal deformity. To maintain skeletal strength and integrity, bone undergoes constant remodeling of its extracellular matrix (ECM) tightly controlled by osteoclast-mediated bone resorption and osteoblast-mediated bone formation. There are at least 20 recognized OI-forms caused by mutations in the two collagen type I-encoding genes or genes implicated in collagen folding, posttranslational modifications or secretion of collagen, osteoblast differentiation and function, or bone mineralization. The underlying disease mechanisms of non-classical forms of OI that are not caused by collagen type I mutations are not yet completely understood, but an altered ECM structure as well as disturbed intracellular homeostasis seem to be the main defects. The ECM orchestrates local cell behavior in part by regulating bioavailability of signaling molecules through sequestration, release and activation during the constant bone remodeling process. Here, we provide an overview of signaling pathways that are associated with known OI-causing genes and discuss the impact of these genes on signal transduction. These pathways include WNT-, RANK/RANKL-, TGFβ-, MAPK- and integrin-mediated signaling as well as the unfolded protein response.*

Etich J, Leßmeier L, Rehberg M, Sill H, Zaucke F, Netzer C, Semler O. **Osteogenesis imperfecta-pathophysiology and therapeutic options.** Mol Cell Pediatr. 2020 Aug 14;7(1):9. doi: 10.1186/s40348-020-00101-9.
Corresponding author: joerg.semler@uk-koeln.de
Abstract: *Osteogenesis imperfecta (OI) is a rare congenital disease with a wide spectrum of severity characterized by skeletal deformity and increased bone fragility as well as additional, variable extraskeletal symptoms. Here, we present an overview of the genetic heterogeneity and pathophysiological background of OI as well as OI-related bone fragility disorders and highlight current therapeutic options.The most common form of OI is caused by mutations in the two collagen type I genes. Stop mutations usually lead to reduced collagen amount resulting in a mild phenotype, while missense mutations mainly provoke structural alterations in the collagen protein and entail a more severe phenotype. Numerous other causal genes have been identified during the last decade that are involved in collagen biosynthesis, modification and secretion, the differentiation and function of osteoblasts, and the maintenance of bone homeostasis.Management of patients with OI involves medical treatment by bisphosphonates as the most promising therapy to inhibit bone resorption and thereby facilitate bone formation. Surgical treatment ensures pain reduction and healing without an increase of deformities. Timely remobilization and regular strengthening of the muscles by physiotherapy are crucial to improve mobility, prevent muscle wasting and avoid bone resorption caused by immobilization. Identification of the pathomechanism for SERPINF1 mutations led to the development of a tailored mechanism-based therapy using denosumab, and unraveling further pathomechanisms will likely open new avenues for innovative treatment approaches.*

Fahim SA, Abdullah MS, Espinoza-Sánchez NA, Hassan H, Ibrahim AM, Ahmed SH, Shakir G, Badawy MA, Zakhary NI, Greve B, El-Shinawi M, Götte M, Ibrahim SA. **Inflammatory Breast Carcinoma: Elevated microRNA miR-181b-5p and Reduced miR-200b-3p, miR-200c-3p, and miR-203a-3p Expression as Potential Biomarkers with Diagnostic Value.** Biomolecules. 2020 Jul 16;10(7):1059. doi: 10.3390/biom10071059.
Corresponding author: mgotte@uni-muenster.de
Abstract: *Inflammatory breast cancer (IBC) is a rare yet aggressive breast cancer variant, associated with a poor prognosis. The major challenge for IBC is misdiagnosis due to the lack of molecular biomarkers. We profiled dysregulated expression of microRNAs (miRNAs) in primary samples of IBC and non-IBC tumors using human breast cancer miRNA PCR array. We discovered that 28 miRNAs were dysregulated (10 were upregulated, while 18 were underexpressed) in IBC vs. non-IBC tumors. We identified 128 hub genes, which are putative targets of the differentially expressed miRNAs and modulate important cancer biological processes. Furthermore, our qPCR analysis independently verified a significantly upregulated expression of miR-181b-5p, whereas a significant downregulation of miR-200b-3p, miR-200c-3p, and miR-203a-3p was detected in IBC tumors. Receiver operating*

characteristic (ROC) curves implied that the four miRNAs individually had a diagnostic accuracy in discriminating patients with IBC from non-IBC and that miR-203a-3p had the highest diagnostic value with an AUC of 0.821. Interestingly, a combination of miR-181b-5p, miR-200b-3p, and miR-200c-3p robustly improved the diagnostic accuracy, with an area under the curve (AUC) of 0.897. Intriguingly, qPCR revealed that the expression of zinc finger E box-binding homeobox 2 (ZEB2) mRNA, the putative target of miR-200b-3p, miR-200c-3p, and miR-203a-3p, was upregulated in IBC tumors. Overall, this study identified a set of miRNAs serving as potential biomarkers with diagnostic relevance for IBC.

. Georgieva VS, Etich J, Bluhm B, Zhu M, Frie C, Wilson R, Zaucke F, Bateman J, Brachvogel B. **Ablation of the miRNA Cluster 24 Has Profound Effects on Extracellular Matrix Protein Abundance in Cartilage.** Int J Mol Sci. 2020 Jun 9;21(11):4112. doi: 10.3390/ijms21114112.
Corresponding author: bent.brachvogel@uni-koeln.de
Abstract: *MicroRNAs (miRNAs) regulate cartilage differentiation and contribute to the onset and progression of joint degeneration. These small RNA molecules may affect extracellular matrix organization (ECM) in cartilage, but for only a few miRNAs has this role been defined in vivo. Previously, we showed that cartilage-specific genetic ablation of the Mirc24 cluster in mice leads to impaired cartilage development due to increased RAF/MEK/ERK pathway activation. Here, we studied the expression of the cluster in cartilage by LacZ reporter gene assays and determined its role for extracellular matrix homeostasis by proteome and immunoblot analysis. The cluster is expressed in prehypertrophic/hypertrophic chondrocytes of the growth plate and we now show that the cluster is also highly expressed in articular cartilage. Cartilage-specific loss of the cluster leads to increased proteoglycan 4 and matrix metallopeptidase 13 levels and decreased aggrecan and collagen X levels in epiphyseal cartilage. Interestingly, these changes are linked to a decrease in SRY-related HMG box-containing (SOX) transcription factors 6 and 9, which regulate ECM production in chondrocytes. Our data suggests that the Mirc24 cluster is important for ECM homoeostasis and the expression of transcriptional regulators of matrix production in cartilage.*

Gerarduzzi C, Hartmann U, Leask A, Drobetsky E. **The Matrix Revolution: Matricellular Proteins and Restructuring of the Cancer Microenvironment.** Cancer Res. 2020 Jul 1;80(13):2705-2717. doi: 10.1158/0008-5472.CAN-18-2098.
Corresponding author: casimiro.gerarduzzi@umontreal.ca
Abstract: *The extracellular matrix (ECM) surrounding cells is indispensable for regulating their behavior. The dynamics of ECM signaling are tightly controlled throughout growth and development. During tissue remodeling, matricellular proteins (MCP) are secreted into the ECM. These factors do not serve classical structural roles, but rather regulate matrix proteins and cell-matrix interactions to influence normal cellular functions. In the tumor microenvironment, it is becoming increasingly clear that aberrantly expressed MCPs can support multiple hallmarks of carcinogenesis by interacting with various cellular components that are coupled to an array of downstream signals. Moreover, MCPs also reorganize the biomechanical properties of the ECM to accommodate metastasis and tumor colonization. This realization is stimulating new research on MCPs as reliable and accessible biomarkers in cancer, as well as effective and selective therapeutic targets.*

Grässel S, Muschter D. **Recent advances in the treatment of osteoarthritis.** F1000Res. 2020 May 4;9:F1000 Faculty Rev-325. doi: 10.12688/f1000research.22115.1. eCollection 2020.
Corresponding author: susanne.graessel@klinik.uni-regensburg.de
Abstract: *Osteoarthritis (OA) is one of the most debilitating diseases and is associated with a high personal and socioeconomic burden. So far, there is no therapy available that effectively arrests structural deterioration of cartilage and bone or is able to successfully reverse any of the existing structural defects. Efforts to identify more tailored treatment options led to the development of strategies that enabled the classification of patient*

subgroups from the pool of heterogeneous phenotypes that display distinct common characteristics. To this end, the classification differentiates the structural endotypes into cartilage and bone subtypes, which are predominantly driven by structure-related degenerative events. In addition, further classifications have highlighted individuals with an increased inflammatory contribution (inflammatory phenotype) and pain-driven phenotypes as well as senescence and metabolic syndrome phenotypes. Most probably, it will not be possible to classify individuals by a single definite subtype, but it might help to identify groups of patients with a predominant pathology that would more likely benefit from a specific drug or cell-based therapy. Current clinical trials addressed mainly regeneration/repair of cartilage and bone defects or targeted pro-inflammatory mediators by intra-articular injections of drugs and antibodies. Pain was treated mostly by antagonizing nerve growth factor (NGF) activity and its receptor tropomyosin-related kinase A (TrkA). Therapies targeting metabolic disorders such as diabetes mellitus and senescence/aging-related pathologies are not specifically addressing OA. However, none of these therapies has been proven to modify disease progression significantly or successfully prevent final joint replacement in the advanced disease stage. Within this review, we discuss the recent advances in phenotype-specific treatment options and evaluate their applicability for use in personalized OA therapy.

. Grobe K, Guerrero I. **Dally-like Is Unlike Dally in Assisting Wingless Spread**. Dev Cell. 2020 Sep 14;54(5):572-573. doi: 10.1016/j.devcel.2020.08.011.
Corresponding author: kgrobe@uni-muenster.de and iguerrero@cbm.csic.es
Abstract: *Lipidated morphogens can spread within tissues to regulate cell fate during development or tissue repair. How these insoluble molecules reach distant target cells remains unclear. Reporting in Nature, McGough et al. (2020) reveal the secret of how the cell-surface proteoglycan Dally-like-protein (Dlp) promotes long-range signaling of the palmitoylated morphogen Wingless.*

Hallmann R, Hannocks MJ, Song J, Zhang X, Di Russo J, Luik AL, Burmeister M, Gerwien H, Sorokin L. **The role of basement membrane laminins in vascular function.** Int J Biochem Cell Biol. 2020 Oct;127:105823. doi: 10.1016/j.biocel.2020.105823.
Corresponding author: sorokin@uni-muenster.de
Abstract: *The extracellular matrix is an integral component of the vasculature, contributing to both developmental processes and structural and functional homeostasis. We describe here the types of extracellular matrices that occur in different blood vessel types, ranging from capillaries to veins, venules and arteries, and focus on the endothelial basement membranes and the laminin family of proteins. We summarize data on the molecular composition of endothelial basement membranes, the structure and in vivo expression patterns of the main endothelial laminin isoforms (laminins 411 and 511) and their, to date, deciphered functions in the vasculature. A significant portion of the review focuses on postcapillary venules and leukocyte extravasation and how the endothelial laminins affect adhesion and migration of different leukocyte types, but also how laminins affect endothelial barrier function by modulating expression and localization of endothelial cell-cell junction molecules, and how these effects differ in CNS versus non-CNS tissues. Comparisons are made to small artery dilation in response to shear flow, which has been shown to be dependent on endothelial laminins and junctional complexes. The data discussed support a central role for basement membrane laminins in different aspects of micro- and macro-vessel endothelial function, but also reveal that many open questions remain, including the contribution of perivascular cells which are either embedded or in direct contact with the endothelial cell basement membrane laminins.*

Hedderich J, El Bagdadi K, Angele P, Grässel S, Meurer A, Straub RH, Zaucke F, Jenei-Lanzl Z. **Norepinephrine Inhibits the Proliferation of *Human* Bone Marrow-Derived Mesenchymal Stem Cells via β2-Adrenoceptor-Mediated ERK1/2 and PKA Phosphorylation.** Int J Mol Sci. 2020 May 30;21(11):3924. doi: 10.3390/ijms21113924.

Corresponding author: zsuzsa.jenei-lanzl@friedrichsheim.de
Abstract: *Bone marrow-derived mesenchymal stem cells (BMSCs) represent an alternative to chondrocytes to support cartilage regeneration in osteoarthritis (OA). The sympathetic neurotransmitter norepinephrine (NE) has been shown to inhibit their chondrogenic potential; however, their proliferation capacity under NE influence has not been studied yet. Therefore, we used BMSCs obtained from trauma and OA donors and compared the expression of adrenergic receptors (AR). Then, BMSCs from both donor groups were treated with NE, as well as with combinations of NE and α1-, α2- or ß1/2-AR antagonists (doxazosin, yohimbine or propranolol). Activation of AR-coupled signaling was investigated by analyzing ERK1/2 and protein kinase A (PKA) phosphorylation. A similar but not identical subset of ARs was expressed in trauma (α2B-, α2C- and ß2-AR) and OA BMSCs (α2A-, α2B-, and ß2-AR). NE in high concentrations inhibited the proliferation of both trauma and OA BMCSs significantly. NE in low concentrations did not influence proliferation. ERK1/2 as well as PKA were activated after NE treatment in both BMSC types. These effects were abolished only by propranolol. Our results demonstrate that NE inhibits the proliferation and accordingly lowers the regenerative capacity of human BMSCs likely via ß2-AR-mediated ERK1/2 and PKA phosphorylation. Therefore, targeting ß2-AR-signaling might provide novel OA therapeutic options.*

Hendrickx G, Danyukova T, Baranowsky A, Rolvien T, Angermann A, Schweizer M, Keller J, Schröder J, Meyer-Schwesinger C, Muschol N, Paganini C, Rossi A, Amling M, Pohl S, Schinke T. **Enzyme replacement therapy in mice lacking arylsulfatase B targets bone-remodeling cells, but not chondrocytes.** Hum Mol Genet. 2020 Mar 27;29(5):803-816. doi: 10.1093/hmg/ddaa006.

Corresponding author: schinke@uke.de
Abstract: *Mucopolysaccharidosis type VI (MPS-VI), caused by mutational inactivation of the glycosaminoglycan-degrading enzyme arylsulfatase B (Arsb), is a lysosomal storage disorder primarily affecting the skeleton. We have previously reported that Arsb-deficient mice display high trabecular bone mass and impaired skeletal growth. In the present study, we treated them by weekly injection of recombinant human ARSB (rhARSB) to analyze the impact of enzyme replacement therapy (ERT) on skeletal growth and bone remodeling. We found that all bone-remodeling abnormalities of Arsb-deficient mice were prevented by ERT, whereas chondrocyte defects were not. Likewise, histologic analysis of the surgically removed femoral head from an ERT-treated MPS-VI patient revealed that only chondrocytes were pathologically affected. Remarkably, a side-by-side comparison with other cell types demonstrated that chondrocytes have substantially reduced capacity to endocytose rhARSB, together with low expression of the mannose receptor. We finally took advantage of Arsb-deficient mice to establish quantification of chondroitin sulfation for treatment monitoring. Our data demonstrate that bone-remodeling cell types are accessible to systemically delivered rhARSB, whereas the uptake into chondrocytes is inefficient.*

Kleiser S, Nyström A. **Interplay between Cell-Surface Receptors and Extracellular Matrix in Skin.** Biomolecules. 2020 Aug 11;10(8):1170. doi: 10.3390/biom10081170.

Corresponding author: svenja.kleiser@uniklinik-freiburg.de and alexander.nystroem@uniklinik-freiburg.de
Abstract: *Skin consists of the epidermis and dermis, which are connected by a specialized basement membrane-the epidermal basement membrane. Both the epidermal basement membrane and the underlying interstitial extracellular matrix (ECM) created by dermal fibroblasts contain distinct network-forming macromolecules. These matrices play various roles in order to maintain skin homeostasis and integrity. Within this complex interplay of cells and matrices, cell surface receptors play essential roles not only for inside-out and outside-in signaling, but also for establishing mechanical and biochemical properties of skin. Already minor modulations of this multifactorial cross-talk can lead to severe and systemic diseases. In this review, major epidermal and dermal cell surface receptors will be addressed with respect to their interactions with matrix components as well as their roles in fibrotic, inflammatory or tumorigenic skin diseases.*

Köhler A, Mörgelin M, Gebauer JM, Öcal S, Imhof T, Koch M, Nagata K, Paulsson M, Zaucke F, Baumann U, Sengle G. **New specific HSP47 functions in collagen subfamily chaperoning.** FASEB J. 2020 Jul 27. doi: 10.1096/fj.202000570R. Online ahead of print.
Corresponding author: frank.zaucke@friedrichsheim.de and gsengle@uni-koeln.de
Abstract: *Although collagens are the most abundant proteins implicated in various disease pathways, essential mechanisms required for their proper folding and assembly are poorly understood. Heat-shock protein 47 (HSP47), an ER-resident chaperone, was mainly reported to fulfill key functions in folding and secretion of fibrillar collagens by stabilizing pro-collagen triple-helices. In this study, we demonstrate unique functions of HSP47 for different collagen subfamilies. Our results show that HSP47 binds to the N-terminal region of procollagen I and is essential for its secretion. However, HSP47 ablation does not majorly impact collagen VI secretion, but its lateral assembly. Moreover, specific ablation of Hsp47 in murine keratinocytes revealed a new role for the transmembrane collagen XVII triple-helix formation. Incompletely folded collagen XVII C-termini protruding from isolated HSP47 null keratinocyte membrane vesicles could be fully restored upon the application of recombinant HSP47. Thus, our study expands the current view regarding the client repertoire and function of HSP47, as well as emphasizes its importance for transmembrane collagen folding.*

Kumar Katakam S, Tria V, Sim WC, Yip GW, Molgora S, Karnavas T, Elghonaimy EA, Pelucchi P, Piscitelli E, Ibrahim SA, Zucchi I, Reinbold R, Greve B, Götte M. **The heparan sulfate proteoglycan syndecan-1 regulates colon cancer stem cell function via a focal adhesion kinase-Wnt signaling axis.** FEBS J. 2020 May 5. doi: 10.1111/febs.15356.
Corresponding author: greveb@uni-muenster.de and mgotte@uni-muenster.de
Abstract: In colon cancer, downregulation of the transmembrane heparan sulfate proteoglycan syndecan-1 (Sdc-1) is associated with increased invasiveness, metastasis, and dedifferentiation. As Sdc-1 modulates signaling pathways relevant to stem cell function, we tested the hypothesis that it may regulate a tumor-initiating cell phenotype. Sdc-1 small-interfering RNA knockdown in the human colon cancer cell lines Caco2 and HT-29 resulted in an increased side population (SP), enhanced aldehyde dehydrogenase 1 activity, and higher expression of CD133, LGR5, EPCAM, NANOG, SRY (sex-determining region Y)-box 2, KLF2, and TCF4/TCF7L2. Sdc-1 knockdown enhanced sphere formation, cell viability, Matrigel invasiveness, and epithelial-to-mesenchymal transition-related gene expression. Sdc-1-depleted HT-29 xenograft growth was increased compared to controls. Decreased Sdc-1 expression was associated with an increased activation of β1-integrins, focal adhesion kinase (FAK), and wingless-type (Wnt) signaling. Pharmacological FAK and Wnt inhibition blocked the enhanced stem cell phenotype and invasive growth. Sequential flow cytometric SP enrichment substantially enhanced the stem cell phenotype of Sdc-1-depleted cells, which showed increased resistance to doxorubicin chemotherapy and irradiation. In conclusion, Sdc-1 depletion cooperatively enhances activation of integrins and FAK, which then generates signals for increased invasiveness and cancer stem cell properties. Our findings may provide a novel concept to target a stemness-associated signaling axis as a therapeutic strategy to reduce metastatic spread and cancer recurrence. DATABASES: The GEO accession number of the Affymetrix transcriptomic screening is GSE58751.

Katakam SK, Pelucchi P, Cocola C, Reinbold R, Vlodavsky I, Greve B, Götte M. **Syndecan-1-Dependent Regulation of Heparanase Affects Invasiveness, Stem Cell Properties, and Therapeutic Resistance of Caco2 Colon Cancer Cells.** Front Oncol. 2020 May 14;10:774. doi: 10.3389/fonc.2020.00774.
Corresponding author: greveb@uni-muenster.de and mgotte@uni-muenster.de
Abstract: *The heparan sulfate proteoglycan Syndecan-1 binds cytokines, morphogens and extracellular matrix components, regulating cancer stem cell properties and invasiveness. Syndecan-1 is modulated by the heparan sulfate-degrading enzyme heparanase, but the underlying regulatory mechanisms are only poorly understood. In colon cancer pathogenesis, complex changes occur in the expression pattern of Syndecan-1 and heparanase*

during progression from well-differentiated to undifferentiated tumors. Loss of Syndecan-1 and increased expression of heparanase are associated with a change in phenotypic plasticity and an increase in invasiveness, metastasis and dedifferentiation. Here we investigated the regulatory and functional interplay of Syndecan-1 and heparanase employing siRNA-mediated silencing and plasmid-based overexpression approaches in the human colon cancer cell line Caco2. Heparanase expression and activity were upregulated in Syndecan-1 depleted cells. This increase was linked to an upregulation of the transcription factor Egr1, which regulates heparanase at the promoter level. Inhibitor experiments demonstrated an impact of focal adhesion kinase, Wnt and ROCK-dependent signaling on this process. siRNA-depletion of Syndecan-1, and upregulation of heparanase increased the colon cancer stem cell phenotype based on sphere formation assays and phenotypic marker analysis (Side-population, NANOG, KLF4, NOTCH, Wnt, and TCF4 expression). Syndecan-1 depletion increased invasiveness of Caco2 cells in vitro in a heparanase-dependent manner. Finally, upregulated expression of heparanase resulted in increased resistance to radiotherapy, whereas high expression of enzymatically inactive heparanase promoted chemoresistance to paclitaxel and cisplatin. Our findings provide a new avenue to target a stemness-associated signaling axis as a therapeutic strategy to reduce metastatic spread and cancer recurrence.

Lewejohann L, Pallerla SR, Schreiber RS, Gerula J, Grobe K. J **Cerebellar Morphology and Behavioral Profiles in Mice Lacking Heparan Sulfate *Ndst* Gene Function.** J Dev Biol. 2020 Jul 11;8(3):E13. doi: 10.3390/jdb8030013.
Corresponding author: kgrobe@uni-muenster.de
Abstract: *Disruption of the Heparan sulfate (HS)-biosynthetic gene N-acetylglucosamine N-Deacetylase/N-sulfotransferase 1 (Ndst1) during nervous system development causes malformations that are composites of those caused by mutations of multiple HS binding growth factors and morphogens. However, the role of Ndst function in adult brain physiology is less explored. Therefore, we generated mice bearing a Purkinje-cell-specific deletion in Ndst1 gene function by using Cre/loxP technology under the control of the Purkinje cell protein 2 (Pcp2/L7) promotor, which results in HS undersulfation. We observed that mutant mice did not show overt changes in the density or organization of Purkinje cells in the adult cerebellum, and behavioral tests also demonstrated normal cerebellar function. This suggested that postnatal Purkinje cell development and homeostasis are independent of Ndst1 function, or that impaired HS sulfation upon deletion of Ndst1 function may be compensated for by other Purkinje cell-expressed Ndst isoforms. To test the latter possibility, we additionally deleted the second Purkinje-cell expressed Ndst family member, Ndst2. This selectively abolished reproductive capacity of compound mutant female, but not male, mice, suggesting that ovulation, gestation, or female reproductive behavior specifically depends on Ndst-dependent HS sulfation in cells types that express Cre under Pcp2/L7 promotor control.*

Niedermair T, Schirner S, Lasheras MG, Straub RH, Grässel S. **Absence of α-calcitonin gene-related peptide modulates bone remodeling properties of murine osteoblasts and osteoclasts in an age-dependent way.** Mech Ageing Dev. 2020 Jul;189:111265. doi: 10.1016/j.mad.2020.111265.
Corresponding author: susanne.graessel@klinik.uni-regensburg.de
Abstract: *Mice with an overall deletion of the sensory neuropeptide α-calcitonin gene-related peptide (α-CGRP) develop an age-dependent osteopenic bone phenotype. Underlying molecular mechanisms of how αCGRP affects bone cell metabolism are not well understood. This study aims to characterize differences in metabolic parameters of osteoblast-like cells (OB) and differentiated bone marrow-derived macrophages (BMM)/osteoclast (OC) cultures isolated from 3 month (3 m) and 9 month old (9 m) α-CGRP-deficient mice (-/-) and age-matched WT controls. All WT bone cell cultures endogenously produced and secreted α-CGRP. We found higher BMM but reduced OB numbers and reduced OB vitality after isolation from 9 m compared to 3 m mice, independent of genotype. Absence of α-CGRP reduced cell spreading, increased apoptosis rate throughout osteogenic differentiation, and reduced ALP activity during late osteogenic differentiation in 9 m OB-/- cultures, whereas minor effects were found in 3 m OB-/- cultures. Cathepsin K activity was reduced in 3 m OC-/- cultures. On the*

contrary, 9 m OC-/- cells demonstrated increased proliferation and caspase3/7 activity. The absence of α-CGRP influenced bone formation and resorption rate differently in bone cells from 3 and 9 m old mice. In summary we suggest, that an increase of dysfunctional mature osteoblasts might occur during aging and contribute to the development of the osteopenic bone phenotype in mature adult (9 m) α-CGRP-deficient mice.

Nyström A, Kiritsi D. **Transmembrane collagens-Unexplored mediators of epidermal-dermal communication and tissue homeostasis.** Exp Dermatol. 2020 Aug 31. doi: 10.1111/exd.14180.
Corresponding author: alexander.nystroem@uniklinik-freiburg.de
Abstract: *Tissue homeostasis is maintained through constant, dynamic and heterogeneous communication between cells and their microenvironment. Proteins that are at the same time active at the intracellular, cell periphery and deeper extracellular levels possess the ability to, on the individual molecular level, influence the cells and their microenvironment in a bidirectional manner. The transmembrane collagens are a family of such proteins, which are of notable interest for tissue development and homeostasis. In skin, expression of all transmembrane collagens has been reported and deficiency of transmembrane collagen XVII manifests with distinct skin phenotypes. Nevertheless, transmembrane collagens in skin remain understudied despite the association of them with epidermal wound healing and dermal fibrotic processes. Here, we present an overview of transmembrane collagens and put a spotlight on them as regulators of epidermal-dermal communication and as potential players in fibrinogenesis.*

Rehberg M, Azim M, Martakis K, Winzenrieth R, Hoyer-Kuhn H, Schoenau E, Semler O, Duran I. **Bone Microarchitecture Assessed by Trabecular Bone Score Is Independent of Mobility Level or Height in Pediatric Patients with Cerebral Palsy.** J Bone Miner Res. 2020 Sep;35(9):1685-1694. doi: 10.1002/jbmr.4047.
Corresponding author: mirko.rehberg@uk-koeln.de
Abstract: *Bone strength and fracture risk do not only depend on bone density, but also on bone structure. The trabecular bone score (TBS) evaluates homogeneity of bone microarchitecture indirectly by measuring gray-level variations of two-dimensional (2D) DXA images. Although TBS is well-established for adults, there have been only few publications in pediatrics. In this monocentric retrospective analysis, we investigated TBS in children and adolescents with cerebral palsy (CP), a patient group vulnerable to low bone mineral mass due to impaired mobility. The influence of different parameters on TBS and areal BMD (aBMD) were evaluated, as well as the relationship between TBS and aBMD. We compared TBS values of our study population to a reference population. A total of 472 lumbar spine–dual-energy X-ray absorptiometry (LS-DXA) scans of children and adolescents with CP (205 female), aged between 4 and 18 years, were analyzed. The DXA-scans were part of the routine examination. The children had no records of fractures or specific bone diseases. Our study population with CP had similar TBS as the reference population. TBS did not increase with age until an inflection point at 10 years in females, and 12 years in males. Girls had significantly higher TBS than boys (p = .049) and pubertal girls aged 8 to 13 years had significantly higher TBS than prepubertal girls (p = .009). TBS standard deviation score for age (SDS-TBS) and aBMD Z-scores correlated weakly (p < .001; R = 0.276 [males], R = 0.284 [females]). Other than for aBMD Z-scores, SDS-TBS was not influenced by age-adjusted height Z-scores and there was no significant difference in SDS-TBS when grouped by mobility levels, using the Gross Motor Function Classification System (GMFCS). Our results indicate that children with CP have a similar homogeneous distribution of trabecular microarchitecture as controls. Puberty initiation appears to be essential for increase of TBS with age and for sex differences. TBS seems less influenced by body composition, height, and mobility than aBMD.*

Rezaei M, Martins Cavaco AC, Stehling M, Nottebaum A, Brockhaus K, Caliandro MF, Schelhaas S, Schmalbein F, Vestweber D, Eble JA. **Extracellular Vesicle Transfer from Endothelial Cells Drives VE-Cadherin Expression in**

Breast Cancer Cells, Thereby Causing Heterotypic Cell Contacts. Cancers (Basel). 2020 Aug 1;12(8):2138. doi: 10.3390/cancers12082138.
Corresponding author: johannes.eble@uni-muenster.de
Abstract: *Cadherins mediate cohesive contacts between isotypic cells by homophilic interaction and prevent contact between heterotypic cells. Breast cancer cells neighboring endothelial cells (ECs) atypically express vascular endothelial (VE)-cadherin. To understand this EC-induced VE-cadherin expression in breast cancer cells, MCF7 and MDA-MB-231 cells expressing different endogenous cadherins were co-cultured with ECs and analyzed for VE-cadherin at the transcriptional level and by confocal microscopy, flow cytometry, and immunoblotting. After losing their endogenous cadherins and neo-expression of VE-cadherin, these cells integrated into an EC monolayer without compromising the barrier function instantly. However, they induced the death of nearby ECs. EC-derived extracellular vesicles (EVs) contained soluble and membrane-anchored forms of VE-cadherin. Only the latter was re-utilized by the cancer cells. In a reporter gene assay, EC-adjacent cancer cells also showed a juxtacrine but no paracrine activation of the endogenous VE-cadherin gene. This cadherin switch enabled intimate contact between cancer and endothelial cells in a chicken chorioallantoic membrane tumor model showing vasculogenic mimicry (VM). This EV-mediated, EC-induced cadherin switch in breast cancer cells and the neo-expression of VE-cadherin mechanistically explain the mutual communication in the tumor microenvironment. Hence, it may be a target to tackle VM, which is often found in breast cancers of poor prognosis.*

Sachs W, Sachs M, Krüger E, Zielinski S, Kretz O, Huber TB, Baranowsky A, Westermann LM, Voltolini Velho R, Ludwig NF, Yorgan TA, Di Lorenzo G, Kollmann K, Braulke T, Schwartz IV, Schinke T, Danyukova T, Pohl S, Meyer-Schwesinger C. **Distinct Modes of Balancing Glomerular Cell Proteostasis in Mucolipidosis Type II and III Prevent Proteinuria.** J Am Soc Nephrol. 2020 Aug;31(8):1796-1814. doi: 10.1681/ASN.2019090960.
Corresponding author: c.meyer-schwesinger@uke.de and s.pohl@uke.de
Abstract: *Background: The mechanisms balancing proteostasis in glomerular cells are unknown. Mucolipidosis (ML) II and III are rare lysosomal storage disorders associated with mutations of the Golgi-resident GlcNAc-1-phosphotransferase, which generates mannose 6-phosphate residues on lysosomal enzymes. Without this modification, lysosomal enzymes are missorted to the extracellular space, which results in lysosomal dysfunction of many cell types. Patients with MLII present with severe skeletal abnormalities, multisystemic symptoms, and early death; the clinical course in MLIII is less progressive. Despite dysfunction of a major degradative pathway, renal and glomerular involvement is rarely reported, suggesting organ-specific compensatory mechanisms. Methods: MLII mice were generated and compared with an established MLIII model to investigate the balance of protein synthesis and degradation, which reflects glomerular integrity. Proteinuria was assessed in patients. High-resolution confocal microscopy and functional assays identified proteins to deduce compensatory modes of balancing proteostasis. Results: Patients with MLII but not MLIII exhibited microalbuminuria. MLII mice showed lysosomal enzyme missorting and several skeletal alterations, indicating that they are a useful model. In glomeruli, both MLII and MLIII mice exhibited reduced levels of lysosomal enzymes and enlarged lysosomes with abnormal storage material. Nevertheless, neither model had detectable morphologic or functional glomerular alterations. The models rebalance proteostasis in two ways: MLII mice downregulate protein translation and increase the integrated stress response, whereas MLIII mice upregulate the proteasome system in their glomeruli. Both MLII and MLIII downregulate the protein complex mTORC1 (mammalian target of rapamycin complex 1) signaling, which decreases protein synthesis. Conclusions: Severe lysosomal dysfunction leads to microalbuminuria in some patients with mucolipidosis. Mouse models indicate distinct compensatory pathways that balance proteostasis in MLII and MLIII.*

Schönborn K, Willenborg S, Schulz JN, Imhof T, Eming SA, Quondamatteo F, Brinckmann J, Niehoff A, Paulsson M, Koch M, Eckes B, Krieg T. **Role of collagen XII in skin homeostasis and repair.** Matrix Biol. 2020 Sep 2:S0945-053X(20)30087-1

Corresponding author: thomas.krieg@uni-koeln.de

Abstract: *Skin integrity and function depends to a large extent on the composition of the extracellular matrix, which regulates tissue organization. Collagen XII is a homotrimer with short collagenous domains that confer binding to the surface of collagen I-containing fibrils and extended flexible arms, which bind to non-collagenous matrix components. Thereby, collagen XII helps to maintain collagen suprastructure and to absorb stress. Mutant or absent collagen XII leads to reduced muscle and bone strength and lax skin, whereas increased collagen XII amounts are observed in tumor stroma, scarring and fibrosis. This study aimed at uncovering in vivo mechanisms by which collagen XII may achieve these contrasting outcomes. We analyzed skin as a model tissue that contains abundant fibrils, composed of collagen I, III and V with collagen XII decorating their surface, and which is subject to mechanical stress. The impact of different collagen XII levels was investigated in collagen XII-deficient (Col12-KO) mice and in mice with collagen XII overexpression in the dermis (Col12-OE). Unchallenged skin of these mice was histologically inconspicuous, but at the ultrastructural level revealed distinct aberrations in collagen network suprastructure. Repair of excisional wounds deviated from controls in both models by delayed healing kinetics, which was, however, caused by completely different mechanisms in the two mouse lines. The disorganized matrix in Col12-KO wounds failed to properly sequester TGFβ, resulting in elevated numbers of myofibroblasts. These are, however, unable to contract and remodel the collagen XII-deficient matrix. Excess of collagen XII, in contrast, promotes persistence of M1-like macrophages in the wound bed, thereby stalling the wounds in an early inflammatory stage of the repair process and delaying healing. Taken together, we demonstrate that collagen XII is a key component that assists in orchestrating proper skin matrix structure, controls growth factor availability and regulates cellular composition and function. Together, these functions are pivotal for re-establishing homeostasis after injury.*

Solomon-Degefa H, Gebauer JM, Jeffries CM, Freiburg CD, Meckelburg P, Bird LE, Baumann U, Svergun DI, Owens RJ, Werner JM, Behrmann E, Paulsson M, Wagener R. **Structure of a collagen VI α3 chain VWA domain array: adaptability and functional implications of myopathy causing mutations**. J Biol Chem. 2020 Sep 4;295(36):12755-12771. doi: 10.1074/jbc.RA120.014865.

Corresponding author: raimund.wagener@uni-koeln.de

Abstract: *Collagen VI is a ubiquitous heterotrimeric protein of the extracellular matrix (ECM) that plays an essential role in the proper maintenance of skeletal muscle. Mutations in collagen VI lead to a spectrum of congenital myopathies, from the mild Bethlem myopathy to the severe Ullrich congenital muscular dystrophy. Collagen VI contains only a short triple helix and consists primarily of von Willebrand factor type A (VWA) domains, protein-protein interaction modules found in a range of ECM proteins. Disease-causing mutations occur commonly in the VWA domains, and the second VWA domain of the α3 chain, the N2 domain, harbors several such mutations. Here, we investigate structure-function relationships of the N2 mutations to shed light on their possible myopathy mechanisms. We determined the X-ray crystal structure of N2, combined with monitoring secretion efficiency in cell culture of selected N2 single-domain mutants, finding that mutations located within the central core of the domain severely affect secretion efficiency. In longer α3 chain constructs, spanning N6-N3, small-angle X-ray scattering demonstrates that the tandem VWA array has a modular architecture and samples multiple conformations in solution. Single-particle EM confirmed the presence of multiple conformations. Structural adaptability appears intrinsic to the VWA domain region of collagen VI α3 and has implications for binding interactions and modulating stiffness within the ECM.*

Strunz M, Simon LM, Ansari M, Kathiriya JJ, Angelidis I, Mayr CH, Tsidiridis G, Lange M, Mattner LF, Yee M, Ogar P, Sengupta A, Kukhtevich I, Schneider R, Zhao Z, Voss C, Stoeger T, Neumann JHL, Hilgendorff A, Behr J, O'Reilly M, Lehmann M, Burgstaller G, Königshoff M, Chapman HA, Theis FJ, Schiller HB. **Alveolar regeneration through a Krt8+ transitional stem cell state that persists in human lung fibrosis.** Nat Commun. 2020 Jul 16;11(1):3559. doi: 10.1038/s41467-020-17358-3.

Corresponding author: herbert.schiller@helmholtz-muenchen.de

Abstract: *The cell type specific sequences of transcriptional programs during lung regeneration have remained elusive. Using time-series single cell RNA-seq of the bleomycin lung injury model, we resolved transcriptional dynamics for 28 cell types. Trajectory modeling together with lineage tracing revealed that airway and alveolar stem cells converge on a unique Krt8 + transitional stem cell state during alveolar regeneration. These cells have squamous morphology, feature p53 and NFkB activation and display transcriptional features of cellular senescence. The Krt8+ state appears in several independent models of lung injury and persists in human lung fibrosis, creating a distinct cell-cell communication network with mesenchyme and macrophages during repair. We generated a model of gene regulatory programs leading to Krt8+ transitional cells and their terminal differentiation to alveolar type-1 cells. We propose that in lung fibrosis, perturbed molecular checkpoints on the way to terminal differentiation can cause aberrant persistence of regenerative intermediate stem cell states.*

Teixeira FCOB, Götte M. **Involvement of Syndecan-1 and Heparanase in Cancer and Inflammation.** Adv Exp Med Biol. 2020;1221:97-135. doi: 10.1007/978-3-030-34521-1_4.

Corresponding author: mgotte@uni-muenster.de

Abstract: *The cell surface heparan sulfate proteoglycan Syndecan-1 acts as an important co-receptor for receptor tyrosine kinases and chemokine receptors, and as an adhesion receptor for structural glycoproteins of the extracellular matrix. It serves as a substrate for heparanase, an endo-β-glucuronidase that degrades specific domains of heparan sulfate carbohydrate chains and thereby alters the functional status of the proteoglycan and of Syndecan-1-bound ligands. Syndecan-1 and heparanase show multiple levels of functional interactions, resulting in mutual regulation of their expression, processing, and activity. These interactions are of particular relevance in the context of inflammation and malignant disease. Studies in animal models have revealed a mechanistic role of Syndecan-1 and heparanase in the regulation of contact allergies, kidney inflammation, multiple sclerosis, inflammatory bowel disease, and inflammation-associated tumorigenesis. Moreover, functional interactions between Syndecan-1 and heparanase modulate virtually all steps of tumor progression as defined in the Hallmarks of Cancer. Due to their prognostic value in cancer, and their mechanistic involvement in tumor progression, Syndecan-1 and heparanase have emerged as important drug targets. Data in preclinical models and preclinical phase I/II studies have already yielded promising results that provide a translational perspective.*

Vijaya Kumar A, Brézillon S, Untereiner V, Sockalingum GD, Kumar Katakam S, Mohamed HT, Kemper B, Greve B, Mohr B, Ibrahim SA, Goycoolea FM, Kiesel L, Pavão MSG, Motta JM, Götte M. **HS2ST1-dependent signaling pathways determine breast cancer cell viability, matrix interactions, and invasive behavior.** Cancer Sci. 2020 Jun 23;111(8):2907-22. doi: 10.1111/cas.14539.

Corresponding author: mgotte@uni-muenster.de

Abstract: *Heparan sulfate proteoglycans (HSPGs) act as signaling co-receptors by interaction of their sulfated glycosaminoglycan chains with numerous signaling molecules. In breast cancer, the function of heparan sulfate 2-O-sulfotransferase (HS2ST1), the enzyme mediating 2-O-sulfation of HS, is largely unknown. Hence, a comparative study on the functional consequences of HS2ST1 overexpression and siRNA knockdown was performed in the breast cancer cell lines MCF-7 and MDA-MB-231. HS2ST1 overexpression inhibited Matrigel invasion, while its knockdown reversed the phenotype. Likewise, cell motility and adhesion to fibronectin and laminin were affected by altered HS2ST1 expression. Phosphokinase array screening revealed a general decrease*

in signaling via multiple pathways. Fluorescent ligand binding studies revealed altered binding of fibroblast growth factor 2 (FGF-2) to HS2ST1-expressing cells compared with control cells. HS2ST1-overexpressing cells showed reduced MAPK signaling responses to FGF-2, and altered expression of epidermal growth factor receptor (EGFR), E-cadherin, Wnt-7a, and Tcf4. The increased viability of HS2ST1-depleted cells was reduced to control levels by pharmacological MAPK pathway inhibition. Moreover, MAPK inhibitors generated a phenocopy of the HS2ST1-dependent delay in scratch wound repair. In conclusion, HS2ST1 modulation of breast cancer cell invasiveness is a compound effect of altered E-cadherin and EGFR expression, leading to altered signaling via MAPK and additional pathways.

Zeng-Brouwers J, Pandey S, Trebicka J, Wygrecka M, Schaefer L. **Communications via the Small Leucine-rich Proteoglycans: Molecular Specificity in Inflammation and Autoimmune Diseases.** J Histochem Cytochem. 2020 Jul 6:22155420930303. doi: 10.1369/0022155420930303. Online ahead of print.
Corresponding author: schaefer@med.uni-frankfurt.de
Abstract: *Inflammation is a highly regulated biological response of the immune system that is triggered by assaulting pathogens or endogenous alarmins. It is now well established that some soluble extracellular matrix constituents, such as small leucine-rich proteoglycans (SLRPs), can act as danger signals and trigger aseptic inflammation by interacting with innate immune receptors. SLRP inflammatory signaling cascade goes far beyond its canonical function. By choosing specific innate immune receptors, coreceptors, and adaptor molecules, SLRPs promote a switch between pro- and anti-inflammatory signaling, thereby determining disease resolution or chronification. Moreover, by orchestrating signaling through various receptors, SLRPs fine-tune inflammation and, despite their structural homology, regulate inflammatory processes in a molecule-specific manner. Hence, the overarching theme of this review is to highlight the molecular and functional specificity of biglycan-, decorin-, lumican-, and fibromodulin-mediated signaling in inflammatory and autoimmune diseases.*

Zhang X, Wang Y, Song J, Gerwien H, Chuquisana O, Chashchina A, Denz C, Sorokin L. **The endothelial basement membrane acts as a checkpoint for entry of pathogenic T cells into the brain.** J Exp Med. 2020 Jul 6;217(7):e20191339. doi: 10.1084/jem.20191339.
Corresponding author: sorokin@uni-muenster.de
Abstract: *The endothelial cell basement membrane (BM) is a barrier to migrating leukocytes and a rich source of signaling molecules that can influence extravasating cells. Using mice lacking the major endothelial BM components, laminin 411 or 511, in murine experimental autoimmune encephalomyelitis (EAE), we show here that loss of endothelial laminin 511 results in enhanced disease severity due to increased T cell infiltration and altered polarization and pathogenicity of infiltrating T cells. In vitro adhesion and migration assays reveal higher binding to laminin 511 than laminin 411 but faster migration across laminin 411. In vivo and in vitro analyses suggest that integrin α6β1- and αvβ1-mediated binding to laminin 511-high sites not only holds T cells at such sites but also limits their differentiation to pathogenic Th17 cells. This highlights the importance of the interface between the endothelial monolayer and the underlying BM for modulation of immune cell phenotype.*

Tiina Petäistö, David Vicente, Kari A Mäkelä, Mikko A Finnilä, Ilkka Miinalainen, Jarkko Koivunen, Valerio Izzi, Mari Aikio, Sanna-Maria Karppinen, Raman Devarajan, Jerome Thevenot, Karl-Heinz Herzig, Ritva Heljasvaara, and Taina Pihlajaniemi. **Lack of collagen XVIII leads to lipodystrophy and perturbs hepatic glucose and lipid homeostasis.** J Physiol. 2020 Aug;598(16):3373-3393
Corresponding author: taina.pihlajaniemi@oulu.fi
Abstract: Liver and adipose tissues play important roles in the regulation of systemic glucose and lipid metabolism. Extracellular matrix synthesis and remodelling are significantly altered in these tissues in obesity and type 2 diabetes. Collagen XVIII is a ubiquitous extracellular matrix component, and it occurs in three isoforms

which differ in terms of molecular size, domain structure and tissue distribution. We recently showed that, in mice, the lack of collagen XVIII, and especially its medium and long isoforms, leads to reduced adiposity and dyslipidaemia. To address the metabolic consequences of these intriguing observations, we assessed whole-body glucose homeostasis in mice challenged with a high-fat diet and in normal physiological conditions. We observed that, in the high caloric diet, the overall adiposity was decreased by 30%, serum triglyceride values were threefold higher and the steatotic area in liver was twofold larger in collagen XVIII knockout mice compared with controls. We demonstrated that mice lacking either all three collagen XVIII isoforms, or specifically, the medium and long isoforms develop insulin resistance and glucose intolerance. Furthermore, we found that ablation of collagen XVIII leads to increased heat production in low temperatures and to reduction of the high blood triglyceride levels of the knockout mice to the level of wild-type mice. Our data indicate that collagen XVIII plays a role in the regulation of glucose tolerance, insulin sensitivity and lipid homeostasis, principally through its ability to regulate the expansion of the adipose tissue. These findings advance the understanding of metabolic disorders.

Nuria Barber-Pérez, Maria Georgiadou, Camilo Guzmán, Aleksi Isomursu, Hellyeh Hamidi, and Johanna Ivaska. **Mechano-responsiveness of fibrillar adhesions on stiffness-gradient gels.** J Cell Sci. 2020 Jun 22;133(12):jcs242909

Corresponding author: johanna.ivaska@utu.fi

Abstract: *Fibrillar adhesions are important structural and adhesive components in fibroblasts, and are required for fibronectin fibrillogenesis. While nascent and focal adhesions are known to respond to mechanical cues, the mechanoresponsive nature of fibrillar adhesions remains unclear. Here, we used ratiometric analysis of paired adhesion components to determine an appropriate fibrillar adhesion marker. We found that active α5β1-integrin exhibits the most definitive fibrillar adhesion localization compared to other proteins, such as tensin-1, reported to be in fibrillar adhesions. To elucidate the mechanoresponsiveness of fibrillar adhesions, we designed a cost-effective and reproducible technique to fabricate physiologically relevant stiffness gradients on thin polyacrylamide (PA) hydrogels, embedded with fluorescently labelled beads. We generated a correlation curve between bead density and hydrogel stiffness, thus enabling a readout of stiffness without the need for specialized knowhow, such as atomic force microscopy (AFM). We find that stiffness promotes growth of fibrillar adhesions in a tensin-1-dependent manner. Thus, the formation of these extracellular matrix-depositing structures is coupled to the mechanical parameters of the cell environment and may enable cells to fine-tune their matrix environment in response to changing physical conditions.*

Michele M Nava, Yekaterina A Miroshnikova, Leah C Biggs, Daniel B Whitefield, Franziska Metge, Jorge Boucas, Helena Vihinen, Eija Jokitalo, Xinping Li, Juan Manuel García Arcos, Bernd Hoffmann, Rudolf Merkel, Carien M Niessen, Kris Noel Dahl, and Sara A Wickström. **Heterochromatin-Driven Nuclear Softening Protects the Genome against Mechanical Stress-Induced Damage.** Cell. 2020 May 14;181(4):800-817.

Corresponding author: sara.wickstrom@helsinki.fi

Abstract: *Tissue homeostasis requires maintenance of functional integrity under stress. A central source of stress is mechanical force that acts on cells, their nuclei, and chromatin, but how the genome is protected against mechanical stress is unclear. We show that mechanical stretch deforms the nucleus, which cells initially counteract via a calcium-dependent nuclear softening driven by loss of H3K9me3-marked heterochromatin. The resulting changes in chromatin rheology and architecture are required to insulate genetic material from mechanical force. Failure to mount this nuclear mechanoresponse results in DNA damage. Persistent, high-amplitude stretch induces supracellular alignment of tissue to redistribute mechanical energy before it reaches the nucleus. This tissue-scale mechanoadaptation functions through a separate pathway mediated by cell-cell contacts and allows cells/tissues to switch off nuclear mechanotransduction to restore initial chromatin state. Our work identifies an*

unconventional role of chromatin in altering its own mechanical state to maintain genome integrity in response to deformation.

Albacete-Albacete L, Navarro-Lérida I, López JA, Martín-Padura I, Astudillo AM, Ferrarini A, Van-der-Heyden M, Balsinde J, Orend G, Vázquez J, del Pozo MA. **ECM deposition is driven by caveolin1-dependent regulation of exosomal biogenesis and cargo sorting.** J Cell Biol, in press, DOI 10.1083/jcb.202006178.
Corresponding authors: inavarro@cnic.es and madelpozo@cnic.es
Abstract: *The composition and physical properties of the extracellular matrix (ECM) critically influence tumor progression, but the molecular mechanisms underlying ECM layering are poorly understood. Tumor–stroma interaction critically depends on cell communication mediated by exosomes, small vesicles generated within multivesicular bodies (MVBs). We show that caveolin-1 (Cav1) centrally regulates exosome biogenesis and exosomal protein cargo sorting through the control of cholesterol content at the endosomal compartment/MVBs. Quantitative proteomics profiling revealed that Cav1 is required for exosomal sorting of ECM protein cargo subsets, including Tenascin-C (TnC), and for fibroblast-derived exosomes to efficiently deposit ECM and promote tumor invasion. Cav1-driven exosomal ECM deposition not only promotes local stromal remodeling but also the generation of distant ECM-enriched stromal niches in vivo. Cav1 acts as a cholesterol rheostat in MVBs, determining sorting of ECM components into specific exosome pools and thus ECM deposition. This supports a model by which Cav1 is a central regulatory hub for tumor–stroma interactions through a novel exosome-dependent ECM deposition mechanism.*

Spenlé C*, Loustau T*, Murdamoothoo D, Erne W, Beghelli-de la Forest Divonne S, Veber R, Petti L, Bourdely P, Mörgelin M, Brauchle EM, Cremel G, Randrianarisoa V, Camara A, Rekima S, Schaub S, Nouhen K, Imhof T, Hansen U, Paul N, Carapito R, Pythoud N, Hirschler A, Carapito C, Dumortier H, Mueller CG, Koch M, Schenke-Layland K, Kon S, Sudaka A, Anjuère F, Van Obberghen-Schilling E, Orend G. **Tenascin-C orchestrates an immuno-suppressive microenvironment in oral squamous cell carcinoma.** Cancer Immun Res 2020 8:1122-1138. Cover image.
Corresponding authors: gertraud.orend@inserm.fr and Ellen.VAN-OBBERGHEN@unice.fr
Abstract: *Inherent immune suppression represents a major challenge in the treatment of human cancer. The extracellular matrix molecule tenascin-C promotes cancer by multiple mechanisms, yet the roles of tenascin-C in tumor immunity are incompletely understood. Using a 4NQO-induced oral squamous cell carcinoma (OSCC) model with abundant and absent tenascin-C, we demonstrated that tenascin-C enforced an immune-suppressive lymphoid stroma via CCL21/CCR7 signaling, leading to increased metastatic tumors. Through TLR4, tenascin-C increased expression of CCR7 in CD11c+ myeloid cells. By inducing CCL21 in lymphatic endothelial cells via integrin α9β1 and binding to CCL21, tenascin-C immobilized CD11c+ cells in the stroma. Inversion of the lymph node-to-tumor CCL21 gradient, recruitment of T regulatory cells, high expression of anti-inflammatory cytokines, and matrisomal components were hallmarks of the tenascin-C-instructed lymphoid stroma. Ablation of tenascin-C or CCR7 blockade inhibited the lymphoid immune-suppressive stromal properties, reducing tumor growth, progression, and metastasis. Thus, targeting CCR7 could be relevant in human head and neck tumors, as high tenascin-C expression and an immune-suppressive stroma correlate to poor patient survival.*

Dhaouadi S, Murdamoothoo D, Asma Tounsi A, William Erne W, Benabderrazek R, Benlasfar Z, Hendaoui L, Chiquet-Ehrismann R, Boubaker S, Orend G, Hendaoui I, Bouhaouala-Zahar B. **Generation and characterization of dromedary Tenascin-C and Tenascin-W specific antibodies.** Biochem Biophys Res Commun 2020 530(2):471-478.
Corresponding author: balkiss.bouhaouala@fmt.utm.tn

Abstract: *Tenascin-C (TNC) and tenascin-W (TNW), large hexameric glycoproteins overexpressed in the tumor microenvironment, are useful tumor biomarkers for theranostic applications. For now, polyclonal and monoclonal antibodies, as well as aptamers targeting TNC and TNW have been developed. However, the immunostaining sensitivity of antibodies is very heterogenous. The main aim of this study was to generate antibodies in dromedary that detect TNC and TNW, respectively. We show that immune sera from immunized dromedaries are able to specifically bind native TNC and TNW by ELISA and also to detect TNC and TNW in matrix tracks of mammary tumors by immunostaining. Furthermore, we demonstrate that purified IgG subtypes are able to interact specifically with TNC or TNW by ELISA and immunostaining. These camelid antibodies are a good basis to develop tools for the detection of TNC and TNW in the tumor microenvironment and could potentially have a broader application for early diagnosis of solid cancers.*

Kyriakopoulou K, Riti E, Piperigkou Z, Koutroumanou Sarri K, Bassiony H, Franchi M, Karamanos NK. **EGFR/ERβ-Mediated Cell Morphology and Invasion Capacity Are Associated with Matrix Culture Substrates in Breast Cancer.** Cells 2020, 9, 2256; doi:10.3390/cells9102256.

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

Abstract: *Breast cancer accounts for almost one in four cancer diagnoses in women. Studies in breast cancer patients have identified several molecular markers, indicators of aggressiveness, which help toward more individual therapeutic approaches. In triple-negative breast cancer (TNBC), epidermal growth factor receptor (EGFR) overexpression is associated with increased metastatic potential and worst survival rates. Specifically, abnormal EGFR activation leads to altered matrix metalloproteinases' (MMPs) expression and, hence, extracellular matrix (ECM) degradation, resulting in induced migration and invasion. The use of matrix substrates for cell culture gives the opportunity to mimic the natural growth conditions of the cells and their microenvironment, as well as cell–cell and cell–matrix interactions. The aim of this study was to evaluate the impact of EGFR inhibition, estrogen receptor beta (ERβ) and different matrix substrates [type I collagen and fibronectin (FN)] on the functional properties, expression of MMPs and cell morphology of ERβ-positive TNBC cells and shERβ ones. Our results highlight EGFR as a crucial regulator of the expression and activity levels of MMPs, while ERβ emerges as a mediator of MMP7 and MT1-MMP expression. In addition, the EGFR/ERβ axis impacts the adhesion and invasion potential of breast cancer cells on collagen type I. Images obtained by scanning electron microscope (SEM) from cultures on the different matrix substrates revealed novel observations regarding various structures of breast cancer cells (filopodia, extravesicles, tunneling nanotubes, etc.). Moreover, the significant contribution of EGFR and ERβ in the morphological characteristics of these cells is also demonstrated, hence highlighting the possibility of dual pharmacological targeting*

MATRIX MEETING ANNOUNCEMENTS

THE ANNUAL MEETING 2020 OF THE DUTCH SOCIETY FOR MATRIX BIOLOGY will take place the 5th and the 6th of November in Lunteren (see also www.matrixbiology.nl).

The new president of the society Prof. Janette Buress (j.k.burgess@umcg.nl).
Secretary of the Dutch Society for Matrix Biology (NVMB): Dr. Roberto Narcisi (r.narcisi@erasmusmc.nl)

NVMB Dutch Society for Matrix Biology

The PAN PACIFIC CONNECTIVE TISSUE SOCIETIES SYMPOSIUM 2020

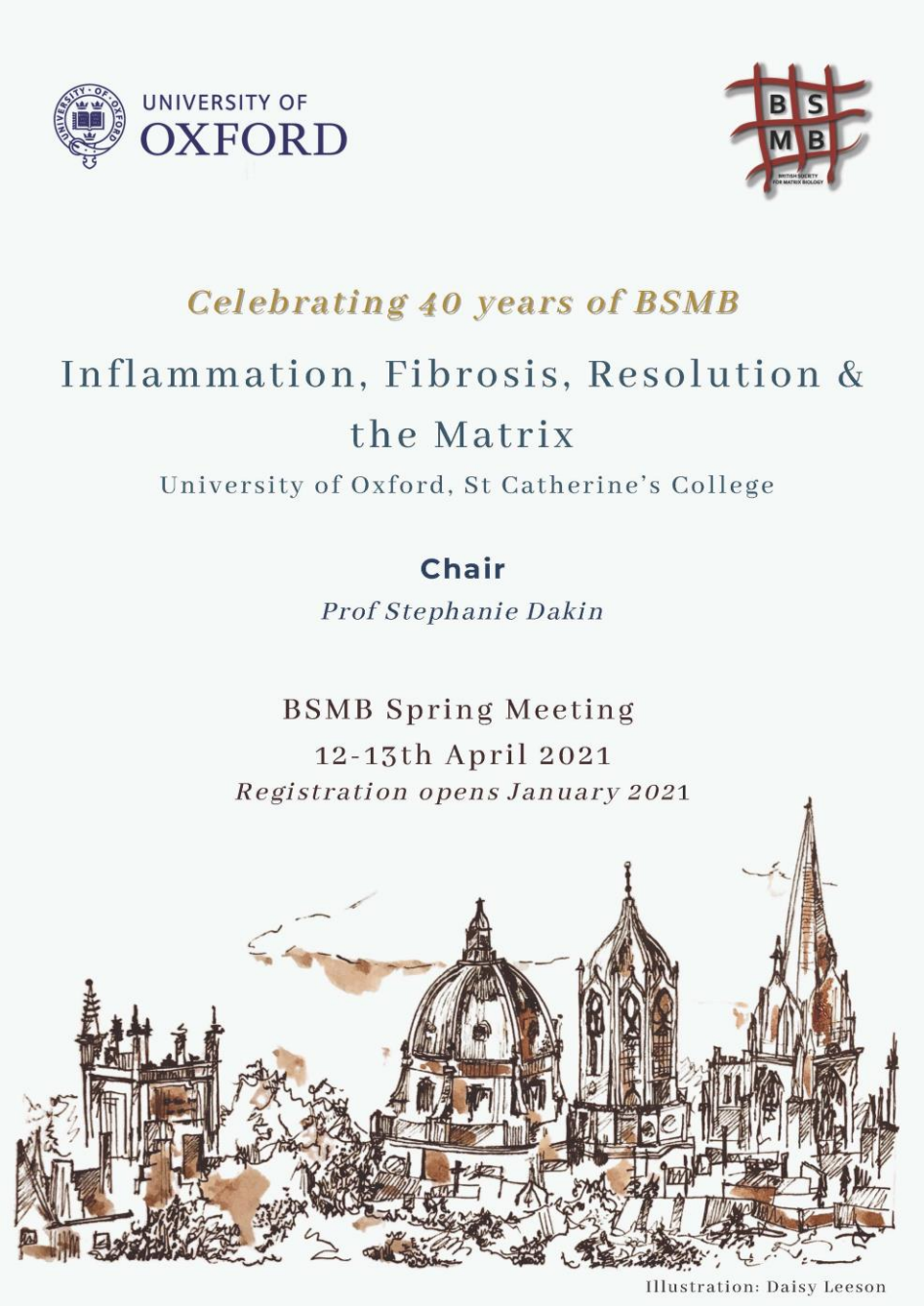
It will be held in conjunction with the scientific meetings of the Australasian Wound & Tissue Repair Society (AWTRS) and the Matrix Biology Society of Australia and New Zealand (MBSANZ). It will take place on November 24 - 26 2020 in Melbourne, Australia.

This meeting will be held in conjunction with the scientific meetings of the Australasian Wound & Tissue Repair Society and the Matrix Biology Society of Australia & New Zealand. The Australasian Wound & Tissue Repair Society (AWTRS) and the Matrix Biology Society of Australia and New Zealand (MBSANZ) are two leading scientific societies focused on the fundamental biological and biochemical mechanisms involved in wound healing and tissue repair and their application in the clinic, as well as the roles of the extracellular matrix in biology and pathology.

ISMB members are entitled to register for the meeting at the members registration rate. In addition, there are a number of conference awards sponsored by ISMB to support conference attendance of graduate research students and early career researchers. Please find more information in the attached documents or on the conference website: https://ppctss2020.smalltalkevents.com.au/

THE BRITISH SOCIETY FOR MATRIX BIOLOGY SPRING MEETING 2020

We are very excited to announce our BSMB Spring 2021 meeting will take place at St Catherine's College, University of Oxford on 12-13th April 2021. The meeting, organised by Prof. Stephanie Dakin will focus on disease mechanisms and translational solutions for the theme 'Inflammation, Fibrosis, Resolution and the Matrix'. The meeting also features the Fell-Muir Lecture awarded to Prof. Andrew Pitsillides. This meeting will celebrate 40 years of BSMB, what better way to celebrate by joining us!



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.

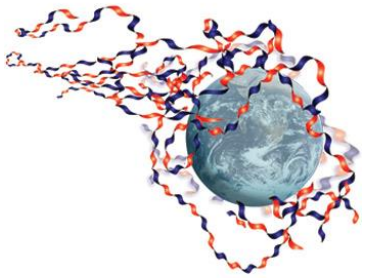
The ASBMB 2020 Meeting should have been held April 4-7 at the San Diego convention center (USA) Along with outstanding award lectures, poster sessions, and workshops, this year six thematic sessions covering foundational areas of biochemistry and molecular biology will meet each of the three mornings 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/

IMPORTANT NOTICE on the INTERNATIONAL SOCIETY FOR HYALURONAN SCIENCES (ISHAS) 2021 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.

2021 COLLAGEN GORDON RESEARCH SEMINAR
July 10-11, 2021
Colby Sawyer College, NH (USA)
Chairs: Delfien Syx & Jonathan A. Roth

2021 COLLAGEN GORDON RESEARCH CONFERENCE
July 11-16, 2021
Colby Sawyer College, NH (USA)
Chair: Taina Pihlajaniemi
Vice Chair: Douglas B. Gould

Gordon Research Conferences
Frontiers of Science

The conference chair is currently developing a list of session titles. This information will be available by September 11, 2020.

RESCHEDULED!!!!!!

The Matrix In Focus: **Matrix, Cells, and Interactions in Health, Disease, Aging, and Regeneration**

NEW DATE: September 12-15, 2021

Hyatt Regency at the Arch, St. Louis, MO (USA)

PROTEOGLYCANS GRS AND GRC, JULY 2022, PROCTOR ACADEMY, ANDOVER, NH (USA)
https://www.grc.org/proteoglycans-conference/2022/

Gordon Research Conference on Proteoglycans 2020: Cancelled… but we are frontiers in proteoglycan research in 2022 again!

Dear Matrix Biology Community,

I would like to kindly inform you due to the global coronavirus pandemic the GRC Board of Trustees has decided to officially close the 2020 Conference on Proteoglycans. This conference is rescheduled for July 2022 in Proctor Academy, NH, USA.

The 2022 conference schedule will be posted by the end of December of this year.
The current chair(s) and vice-chair(s) will remain in place and run the conference in 2022. Applications for 2022 meetings will open at the end of December of this year and you can reapply to the conference at that time.

We will write a new NIH grant to support young investigators in our field.
I would like to take the opportunity to thank all organization and companies to support our meeting. Our budget will be rescheduled for 2022.

I am very grateful to my Co-Chair Charles Frevert for his constant support. I would like to thank all formal GRC Chairs, the Advisory Committee, Chair persons, Speakers, and Participants for their advice, enthusiasm and friendship.
Anyhow this is an honor to be a Chair of the GRC twice!
With your help we will organize the 2022 GRC on Proteoglycans!

Please stay well!!

I am looking forward to give a big hug to all of you in 2022 in Proctor Academy, Andover, NH.

Best wishes,
Liliana Schaefer
Chair of the 2020 & 2022 GRC on Proteoglycans