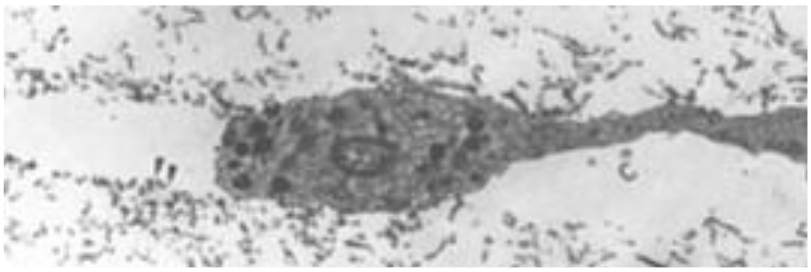


**A fibroblast within a tethered lattice, after 13 days, with a cavity surrounding the cell and areas of packed collagen fibrils** *(Porter et al. 1998 Wound Rep. Reg. 6: 157-166)*

**ISMB NEWSLETTER 38 May 2021 Editor: Sylvie Ricard-Blum**

# FROM THE PRESIDENT'S DESK

Dear Fellow Matrix Biologists:

I hope you are all well, finding your work rewarding and vaccinated or soon to be. The pandemic continues its relentless march across the world, showing that we cannot afford to relax our vigilance nor consideration for those around us. It is a time that calls for calm and patience, but also more than ever, for kindness and optimism. The last is the word I'd like to dwell on in my letter as it is reflected in the content of this issue of the ISMB newsletter. As always, Sylvie has done a wonderful job assembling diverse information sets into a helpful, all-in-one-place format. I see cause for optimism in the high-quality publications you have contributed, the training opportunities, planned activities of the various societies and especially the updates on conferences. Perhaps we can cautiously resume meeting in person in the near future- time will tell, but in the meantime, let's do what we can, where we are, with what we have and keep up the momentum of our field. As part of that approach, please keep sending material for this newsletter. It binds us together, makes the world smaller again.



For the ISMB, I'd like to thank our council, and propose a big thank-you to Valerio Izzi, who has the now grandee title of WebMaster, for taming the ravages of time and obsolescence that had affected our website. It is improving by the day and your suggestions for the site as it continues to develop will be welcomed. A few notification tasks below:

Matrix Biology Plus is now indexed in PubMed Central

Applications for international travel fellowships resume (the next deadline being July 1, 2021) for virtual, hybrid and in-person meetings

ISMB members can purchase volumes of the Springer series, Biology of the Extracellular Matrix, at reduced prices (see the web site for details).

Best wishes.

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

## Content

## Available positions

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

### Post-doctoral position: AI-based analysis of the tumor extracellular matrix
### 3IA Côte d'Azur Research Axis : AI for Computational Biology and Bio-Inspired AI

Applications are invited for a 2-year 3iA Côte d'Azur postdoctoral position in tumor/ECM biology to study functional and structural features of the extracellular matrix (ECM) in the immunosuppressive tumor microenvironment of head and neck cancer. Immunomodulatory therapies are promising for this tumor type, yet resistance rates are high since less than 20% of patients respond. We are specifically interested in exploring the tumor ECM environment, together with immune cell signatures, for gaining mechanistic insights into invasive disease and resistance to immunotherapy. Our previous work on ECM topology based on confocal images of cell-derived ECM has provided a framework for quantitative description and modeling of matrix Features associated with disease states. The present project involves quantitative characterization of ECM architecture in in vitro models and human tumor tissue using multiplex immunofluorescence imaging, empowered by deep learning approaches.

Biological studies will be carried out in the Institute of Biology Valrose, a leading Research Center of the Université Côte d'Azur (UCA) equipped with state-of the-art core facilities and a dynamic scientific environment. Computational analyses will be performed in close collaboration with biological image processing experts of the I3S Laboratory, UCA (MORPHEM group) and clinical partners, thus providing interdisciplinary training at the crossroads of ECM/tumor biology, computational biology and human tumor pathology.

**Profile**: The candidate should be a creative, quantitatively-minded biologist with a strong background in cell/tissue imaging. Previous experience in tumor biology and the ECM are an advantage. Excellent communication skills, both written and oral (English), are required.

**Please send applications (motivation statement, full CV, 2 letters of recommendation including one from PhD thesis advisor)** to **Ellen Van Obberghen-Schilling** (Ellen.Van-Obberghen@unice.fr). Further information is available on the 3IA Côte d'Azur website (https://3ia.univ-cotedazur.eu/apply/call-for-applications-phd-postdoctoral-positions).

**Selected recent publications** of the host team:

Spenlé C et al. Tenascin-C Orchestrates an Immune-Suppressive Tumor Microenvironment in Oral Squamous Cell Carcinoma. **Cancer Immunol Res.** 2020 Sep;8(9):1122-1138.

Efthymiou G et al. Shaping Up the Tumor Microenvironment with Cellular Fibronectin. **Front Oncol.** 2020 Apr 30;10:641.

Efthymiou G et al. Fibronectin Extra Domains tune cellular responses and confer topographically distinct features to fibril networks. **Journal of Cell Science** 2021 : jcs.252957 doi: 10.1242/jcs.252957

## A 2-years post-doctoral position funded by INCa (Institut National du Cancer) is available at MEDyC research unit in Reims (France)
## UMR CNRS 7369, "Extracellular matrix, Cancer and Therapeutic target" team

This INCa-funded project is based on a unique academic-industry R&D partnership gathering together MEDyC unit (CNRS UMR7369), Gustave Roussy Institute and Apmonia Therapeutics, a biotech company dedicated to developing anti-cancer immunotherapy strategies.

The goal of the project is to deeply **investigate the relevance of targeting the TSP-1/CD47 axis in the purpose of restoring anti-tumor immunity in ovarian cancer**, one of the highest unmet medical needs in oncology. We will seek to open new therapeutic perspectives for the treatment of ovarian cancer focusing our attention on an **optimized drug candidate (TAX2)** with highly advanced preclinical characterization.

As a priority, the post-doctoral research scientist will further decipher and characterize the TAX2-mediated immune response (*in vitro* & *in vivo*) to strengthen the proof-of-mechanism for TAX2-related immunomodulation in ovarian cancer. He/She will also contribute to provide a rationale for an optimized therapeutic combination strategy using TAX2 drug candidate.

We are therefore looking for a highly motivated candidate with **significant background in oncoimmunology** (knowledge and technical skills) and **mouse tumor models** (animal experimentation degree is an essential prerequisite).

Ideally, the candidate would have several years of research in the field of **tumor microenvironment** with expertise on extracellular matrix components. The candidate will have to work in close interaction with the two other partners of the project, namely Gustave Roussy Institute and Apmonia Therapeutics R&D team. Organization skills, strength of proposal, team spirit and high level of autonomy are required.

Interested candidates are invited to send a detailed CV with publication list, motivation letter and referees names to Pr. Stéphane Dedieu (stephane.dedieu@univ-reims.fr)

**Key words**: tumor microenvironment, extracellular matrix, immuno-oncology, ovarian cancer, therapeutic combinations.

**FULL PROFESSOR POSITION IN CELL BIOLOGY**

**A Full Professor position in Cell Biology is open at the University of Lyon and within the Tissue Biology and Therapeutic Engineering Laboratory (LBTI, UMR 5305 CNRS** (https://lbti.ibcp.fr/).

The candidate for this position will be a French-speaking cell biologist and will be recruited through a competitive process.

He/She should have a strong expertise (1) in general Cell Biology, for the teaching in Bachelor's degree, and (2) in Tissue Biology, Cell-extracellular Matrix Interactions and/or in Mechanotransduction, for the teaching in the Master program. He/She will be recruited to strengthen the "Tissue repair" axis of the LBTI Unit research. He/She will develop a research project in accordance with the topics that are developed in the research unit, which consist in (1) understanding the fundamental mechanisms of the spatial organization of a 3D tissue, (2) understanding and evaluating tissue response(s) to different extrinsic and intrinsic insults (excluding cancer), and (3) proposing and testing innovative therapeutic approaches in the context of tissue engineering and regenerative medicine. Thus, He/She should have a strong expertise in the study of dynamic cell-cell or cell-microenvironment cross-talks during homeostatis or tissue repair processes.

**Research contact**: Dr. Dominique SIGAUDO-ROUSSEL (dominique.sigaudo-roussel@ibcp.fr)
**Teaching contact**: Prof. Ulrich VALCOURT (ulrich.valcourt@ibcp.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)

In Focus

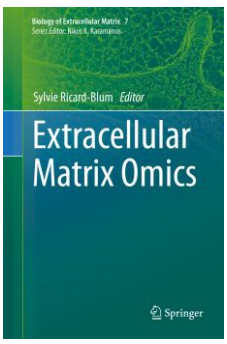
**A novel method for sensor-based quantification of single/multicellular force dynamics and stiffening in 3D matrices.** Emon B, Li Z, Joy MSH, Doha U, Kosari F, Saif MTA Sci Adv. 2021 Apr 9;7(15):eabf2629. doi: 10.1126/sciadv.abf2629.
**Corresponding author**: saif@illinois.edu
**Abstract**: *Cells in vivo generate mechanical traction on the surrounding 3D extracellular matrix (ECM) and neighboring cells. Such traction and biochemical cues may remodel the matrix, e.g., increase stiffness, which, in turn, influences cell functions and forces. This dynamic reciprocity mediates development and tumorigenesis. Currently, there is no method available to directly quantify single-cell forces and matrix remodeling in 3D. Here, we introduce a method to fulfill this long-standing need. We developed a high-resolution microfabricated sensor that hosts a 3D cell-ECM tissue formed by self-assembly. This sensor measures cell forces and tissue stiffness and can apply mechanical stimulation to the tissue. We measured single and multicellular force dynamics of fibroblasts (3T3), human colon (FET) and lung (A549) cancer cells, and cancer-associated fibroblasts (CAF05) with 1-nN resolution. Single cells show notable force fluctuations in 3D. FET/CAF coculture system, mimicking cancer tumor microenvironment, increased tissue stiffness by three times within 24 hours.*

**Generation of a novel mouse strain with fibroblast-specific expression of Cre recombinase.**
Alam J, Musiime M, Romaine A, Sawant M, Melleby AO, Lu N, Eckes B, Christensen G, Gullberg D. Matrix Biol Plus. 2020 Jul 7;8:100045. doi: 10.1016/j.mbplus.2020.100045.
**Corresponding author**: donald.gullberg@uib.no

**Abstract**: *Cell-specific expression of genes offers the possibility to use their promoters to drive expression of Cre-recombinase, thereby allowing for detailed expression analysis using reporter gene systems, cell lineage tracing, conditional gene deletion, and cell ablation. In this context, current data suggest that the integrin α11 subunit has the potential to serve as a fibroblast biomarker in tissue regeneration and pathology, in particular in wound healing and in tissue- and tumor fibrosis. The mesenchyme-restricted expression pattern of integrin α11 thus prompted us to generate a novel ITGA11-driver Cre mouse strain using a ϕC31 integrase-mediated knock-in approach. In this transgenic mouse, the Cre recombinase is driven by regulatory promoter elements within the 3 kb segment of the human ITGA11 gene. β-Galactosidase staining of embryonic tissues obtained from a transgenic ITGA11-Cre mouse line crossed with Rosa 26R reporter mice (ITGA11-Cre;R26R) revealed ITGA11-driven Cre expression and activity in mesenchymal cells in a variety of mesenchymal tissues in a pattern reminiscent of endogenous α11 protein expression in mouse embryos. Interestingly, X-gal staining of mouse embryonic fibroblasts (MEFs) isolated from the ITGA11-Cre;R26R mice indicated heterogeneity in the MEF population. ITGA11-driven Cre activity was shown in approximately 60% of the MEFs, suggesting that the expression of integrin α11 could be exploited for isolation of different fibroblast populations. ITGA11-driven Cre expression was found to be low in adult mouse tissues but was induced in granulation tissue of excisional wounds and in fibrotic hearts following aortic banding. We predict that the ITGA11-Cre transgenic mouse strain described in this report will be a useful tool in matrix research for the deletion of genes in subsets of fibroblasts in the developing mouse and for determining the function of subsets of pro-fibrotic fibroblasts in tissue fibrosis and in different subsets of cancer-associated fibroblasts in the tumor microenvironment.*

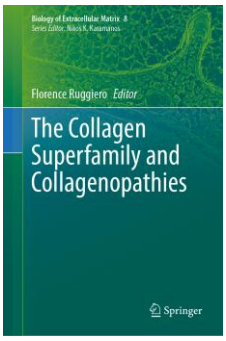
## Books & Special Issues on the Extracellular Matrix

Check out **SPRINGER'S BIOLOGY OF EXTRACELLULAR MATRIX BOOK SERIES**, **published in collaboration with the International Society for Matrix Biology**.




ISMB members receive a 40% discount on all books published in the series. Use discount code ISMB40 when ordering your book via The Springer Shop. Under the new editorship of Nikos Karamanos (University of Patras, Greece), the series is reaching new heights.

Please see the latest volume in the series **Extracellular Matrix Omics** edited by Sylvie Ricard-Blum (University of Lyon, France).




Forthcoming volumes are:
- F. Ruggiero (Ed.) **The Collagen Superfamily and Collagenopathies**
- M. Götte, K. Forsberg-Nilsson (Eds.) **Proteoglycans in Stem Cells**

Topics in the series include cellular differentiation, tissue development and tissue remodeling. Each volume provides an in-depth overview of a particular topic, and offers a reliable source of information for post-graduates and advanced researchers alike.

Do you have questions about the series or the ISMB member discount? Please contact Dr. Miriam Latuske: miriam.latuske@springernature.com

## SPECIAL ISSUE
## EXTRACELLULAR MATRIX: THE DYNAMIC STRUCTURAL AND FUNCTIONAL NETWORK IN HEALTH AND DISEASE

Dear colleagues,

We are spearheading development of a special issue of IUBMB Life, the flagship journal of IUBMB, on the topic of **Extracellular Matrix: The Dynamic Structural and Functional Network in Health and Disease**.

We invite you to contribute original research articles that address the ECM as a key player in health and disease, in cell functional properties and behavior, in disease diagnosis and pharmacological targeting/treatment approaches, as well as in bioengineering and biotechnology. Themes related to development, evolution, tumor biology, therapeutics, -omics and aging are also welcomed. Research approaches could address either ECM networks or macromolecules such as collagens, proteoglycans, glycosaminoglycans, integrins, cell-matrix receptors, matrix-degrading and modifying enzymes and matrix-related proteins/glycoproteins.

Critical reviews in areas not recently covered are also welcomed upon invitation or approval of proposals by the guest editors, Nikos Karamanos (Univ. of Patras, Greece), Sylvie Ricard-Blum (Univ. of Lyon, France), and Dimitris Kletsas (NCSR Demokritos, Athens, Greece).

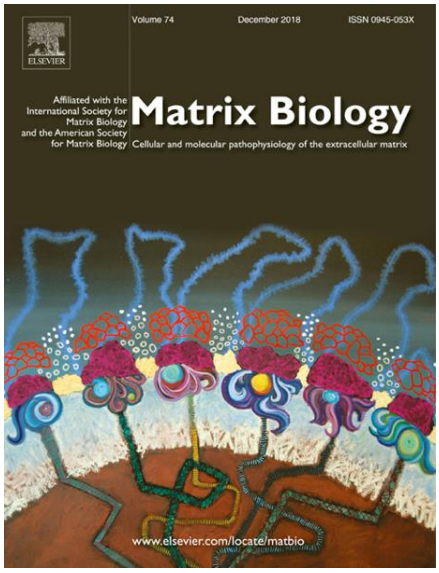
Relevant info regarding the scope, topics and manuscript submission are given below and at: https://iubmb.onlinelibrary.wiley.com/hub/journal/15216551/cfp

**Manuscripts should be submitted by 31 October 2021**.

Submit your manuscript through the IUBMB Life ScholarOne site at https://mc.manuscriptcentral.com/tbmb.

If you have questions about topic suitability, please contact Guest Editor Nikos Karamanos (n.k.karamanos@upatras.gr).

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




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

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

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

In preparation of your submission, please remember the following items:

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

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

Best wishes.

Alexandra Naba, PhD University of Illinois-Chicago (IL, USA)

Suneel S. Apte, MBBS, DPhil, Cleveland Clinic Lerner Research Institute (OH, USA)

## THEmeshwork

### #THEmeshwork: a new way to connect scientists across the world

One fact is that the COVID-19 pandemic challenged scientist in the way they communicate to each other. We were isolated and early career researchers (ECRs) were missing out opportunities to present their work and network. We also realized that we were waiting for in-person meetings to meet and connect with each other and share our science.

**A brand-new initiative well supported:**

With 6 other ECRs we decided to invent a new way to connect scientists with a common interest for the extracellular matrix (ECM). In September 2020, after two intent brainstorming's, we created **#THEmeshwork**.

Our key mission is to bring the spotlight on ECRs and provide a channel for them to communicate their science with the kindly support of well-established researchers. Our second mission is to provide career development support to ECRs by organizing career event to discuss about subjects as broad as grant writing, virtual talk or reviewing process with expert panelists. Finally, we wanted to create a platform to exchange in between meetings to share protocols, advice, job ads, preprints, and newly published papers….

In the past few months, our community grew from 7 idealist ECRs to almost 200 members from PhD students to senior PIs on our slack platform. We organized 3 scientific virtual events, 3 career virtual events, were present in networking sessions at the 2020 ASCB meeting and the 2021 Finnish matrix biology society meeting.

**Beyond the pandemic:**

We are now thinking ahead about the after-pandemic-world. As we want #THEmeswork to be more than a temporary solution, we brainstormed and envisioned a bright future for our community.

First, our slack platform we stay up and running to allow ECRs to exchange in between in-person meetings.

Then, we created a non-profit organization to gather funds to support ECRs and organize in person events for ECRs to meet at the in-person meetings. We aim to collaborate with ECM societies to organize special events for ECRs.

An executive committee was elected for the next 2 years with Julie Di Martino as president, Pauline Nauroy as treasurer and Chloe Yeung as secretary.

**Upcoming events:**

In April, we will hold a scientific virtual event highlighting proteoglycan research and in May, we will participate to the organization of a career session at the French and German societies for matrix biology virtual meeting. Finally, in June we will organize a virtual scientific event on tissue engineering and regenerative medicine before a well-deserved summer break! But stay tuned, we might have summer surprises!

**Join us!**

If you did not do it yet, join us by emailing us at : themeshwork2020@gmail.com.

We thank all the member that join already and actively participate to the life of our online platform and invite you to visit our website for more information. https://themeshwork2020.wixsite.com/info

Written by Julie Di Martino, edited by Pauline Nauroy.

On behalf of #THEmeswork team.

## Recent publications

**Basement membrane stiffness determines metastases formation**. Reuten R, Zendehroud S, Nicolau M, Fleischhauer L, Laitala A, Kiderlen S, Nikodemus D, Wullkopf L, Nielsen SR, McNeilly S, Prein C, Rafaeva M, Schoof EM, Furtwängler B, Porse BT, Kim H, Won KJ, Sudhop S, Zornhagen KW, Suhr F, Maniati E, Pearce OMT, Koch M, Oddershede LB, Van Agtmael T, Madsen CD, Mayorca-Guiliani AE, Bloch W, Netz RR, Clausen-Schaumann H, Erler JT. Nat Mater. 2021 Jan 25. doi: 10.1038/s41563-020-00894-0.
**Corresponding author**: raphael.reuten@bric.ku.dk, janine.erler@bric.ku.dk
**Abstract**: *The basement membrane (BM) is a special type of extracellular matrix and presents the major barrier cancer cells have to overcome multiple times to form metastases. Here we show that BM stiffness is a major determinant of metastases formation in several tissues and identify netrin-4 (Net4) as a key regulator of BM stiffness. Mechanistically, our biophysical and functional analyses in combination with mathematical simulations show that Net4 softens the mechanical properties of native BMs by opening laminin node complexes, decreasing cancer cell potential to transmigrate this barrier despite creating bigger pores. Our results therefore reveal that BM stiffness is dominant over pore size, and that the mechanical properties of 'normal' BMs determine metastases formation and patient survival independent of cancer-mediated alterations. Thus, identifying individual Net4 protein levels within native BMs in major metastatic organs may have the potential to define patient survival even before tumour formation. The ratio of Net4 to laminin molecules determines BM stiffness, such that the more Net4, the softer the BM, thereby decreasing cancer cell invasion activity.*

**Further analyses of APRIL/APRIL-Receptor/Glycosaminoglycan interactions by biochemical assays linked to computational studies**. Mateusz Marcisz, Bertrand Huard, Agnieszka G Lipska, Sergey A Samsonov. Glycobiology cwab016, https://doi.org/10.1093/glycob/cwab016
**Corresponding author**: sergey.samsonov@ug.edu.pl
**Abstract**: A proliferation-inducing ligand (APRIL) is a member of the tumor necrosis factor superfamily. APRIL is quite unique in this superfamily for at least for two reasons: i) it binds to glycosaminoglycans (GAGs) via its positively charged N-terminus; ii) one of its signaling receptor, the transmembrane activator CAML interactor (TACI) was also reported to bind GAGs. Here, as provided by biochemical evidences with the use of an APRIL deletion mutant linked to computational studies, APRIL-GAG interaction involved other regions than the APRIL N-terminus. Preferential interaction of APRIL with heparin followed by chondroitin sulfate E were confirmed by in silico analysis. Both computational and experimental approaches did not reveal heparan sulfate binding to TACI. Together, computational results corroborated experiments contributing with atomistic details to the knowledge on this biologically relevant trimolecular system. Additionally, a high-throughput rigorous analysis of the free energy calculations data was performed to critically evaluate the applied computational methodologies.

**Fabrication, Rheological Characterization and Compositional Proteomics of in-situ Thermoresponsive Hydrogel from Porcine Cornea Extracellular Matrix for Corneal Tissue Engineering Purposes.** Yazdanpanah G, Jiang Y, Rabiee B, Omidi M, Rosenblatt MI, Shokuhfar T, Pan Y, Naba A, and Djalilian AR. Tissue Engineering Part C Methods, 2021. April 3. https://doi.org/10.1089/ten.TEC.2021.0011
**Corresponding author**: adjalili@uic.edu
**Abstract**: *Fabricating thermoresponsive hydrogels from decellularized tissues is a trending and promising approach to develop novel biomaterials for tissue engineering and therapeutic purposes. There are differences in the characteristics of the produced hydrogels related to the source tissue as well as the decellularization and solubilization protocols employed. Detailed characterization of the hydrogels will support the efforts to optimize their application as biomaterials for tissue engineering and therapeutics. Here, we describe an optimized method for fabricating an in-situ thermoresponsive hydrogel from decellularized porcine cornea extracellular matrix (COMatrix), and provide a detailed characterization of its structure, thermoresponsive rheological behavior (heat-*

*induced Sol-Gel transition), as well as exploring its protein composition using proteomics. COMatrix forms a transparent gel (10 minutes time to gelation) after in-situ curing with heat, characterized by alteration in light absorbance and rheological indexes. The rheological characterization of heat-formed COMatrix gel shows similar behavior to common biomaterials utilized in tissue engineering. The fibrillar structure of COMatrix gel was observed by scanning electron microscopy showing that the density of fibers attenuates in lower concentrations. Mass-spectrometry-based proteomic analysis revealed that COMatrix hydrogel is rich in proteins with known regenerative properties such as lumican, keratocan and laminins in addition to structural collagen proteins. COMatrix hydrogel is a naturally-driven biomaterial with favorable biomechanical properties and protein content with potential application as a therapeutic biomaterial in ocular regeneration and tissue engineering*.

**Global proteomic analysis of extracellular matrix in mouse and human brain highlights relevance to cerebrovascular disease**. Pokhilko A, Brezzo G, Heilig R, Lennon R, Smith C, Allan SM, Granata A, Sinha S, Wang T, Markus HS, Naba A, Fischer R, van Agtmael T, Horsburgh K, and Cader ZM. J Cereb Blood Flow Metab. 2021 Mar 17;271678X211004307. doi: 10.1177/0271678X211004307.
**Corresponding authors**: zameel.cader@ndcn.ox.ac.uk, Karen.Horsburgh@ed.ac.uk, tom.vanagtmael@glasgow.ac.uk
**Abstract**: *The extracellular matrix (ECM) is a key interface between the cerebrovasculature and adjacent brain tissues. Deregulation of the ECM contributes to a broad range of neurological disorders. However, despite this importance, our understanding of the ECM composition remains very limited mainly due to difficulties in its isolation. To address this, we developed an approach to extract the cerebrovascular ECM from mouse and human post-mortem normal brain tissues. We then used mass spectrometry with off-line high-pH reversed-phase fractionation to increase the protein detection. This identified more than 1000 proteins in the ECM-enriched fraction, with > 66% of the proteins being common between the species. We report 147 core ECM proteins of the human brain vascular matrisome, including collagens, laminins, fibronectin and nidogens. We next used network analysis to identify the connection between the brain ECM proteins and cerebrovascular diseases. We found that genes related to cerebrovascular diseases, such as COL4A1, COL4A2, VCAN and APOE were significantly enriched in the cerebrovascular ECM network. This provides unique mechanistic insight into cerebrovascular disease and potential drug targets. Overall, we provide a powerful resource to study the functions of brain ECM and highlight a specific role for brain vascular ECM in cerebral vascular disease.*

**The burden of post-translational modification (PTM) - Disrupting mutations in the tumor matrisome**. Holstein E, Dittmann A, Kääriäinen A, Pesola V, Koivunen J, Taina Pihlajaniemi T, Naba A, and Izzi V.
Cancers (Basel) 2021 Mar 3;13(5):1081. doi: 10.3390/cancers13051081.
**Corresponding author**: valerio.izzi@oulu.fi
**Abstract**: *Background: To evaluate the occurrence of mutations affecting post-translational modification (PTM) sites in matrisome genes across different tumor types, in light of their genomic and functional contexts and in comparison with the rest of the genome. Methods: This study spans 9075 tumor samples and 32 tumor types from The Cancer Genome Atlas (TCGA) Pan-Cancer cohort and identifies 151,088 non-silent mutations in the coding regions of the matrisome, of which 1811 affecting known sites of hydroxylation, phosphorylation, N- and O-glycosylation, acetylation, ubiquitylation, sumoylation and methylation PTM. Results: PTM-disruptive mutations (PTMmut) in the matrisome are less frequent than in the rest of the genome, seem independent of cell-of-origin patterns but show dependence on the nature of the matrisome protein affected and the background PTM types it generally harbors. Also, matrisome PTMmut are often found among structural and functional protein regions and in proteins involved in homo- and heterotypic interactions, suggesting potential disruption of matrisome functions. Conclusions: Though quantitatively minoritarian in the spectrum of matrisome mutations, PTMmut show*

*distinctive features and damaging potential which might concur to deregulated structural, functional, and signaling networks in the tumor microenvironment.*

**Computational and experimental characterization of the novel ECM glycoprotein SNED1 and prediction of its interactome.** Vallet SD, Davis MN, Barque A, Thahab AH, Ricard-Blum S, Naba A. Biochem J. 2021 Mar 16:BCJ20200675. doi: 10.1042/BCJ20200675.
**Corresponding authors:** sylvie.ricard-blum@univ-lyon1.fr and anaba@uic.edu
**Abstract**: *The extracellular matrix (ECM) is a complex meshwork of proteins and an essential component of multicellular life. We have recently reported the characterization of a novel ECM protein, SNED1, and showed that it promotes breast cancer metastasis and regulates craniofacial development. However, the mechanisms by which it does so remain unknown. ECM proteins exert their functions by binding to cell surface receptors and interacting with other ECM proteins, actions that we can predict using knowledge of protein's sequence, structure, and post-translational modifications. Here, we combined in-silico and in-vitro approaches to characterize the physico-chemical properties of SNED1 and infer its putative functions. To do so, we established a mammalian cell system to produce and purify SNED1 and its N-terminal fragment, which contains a NIDO domain and demonstrated experimentally SNED1's potential to be glycosylated, phosphorylated, and incorporated into an insoluble ECM. We also determined the secondary and tertiary structures of SNED1 and its N-terminal fragment and obtained a model for its NIDO domain. Using computational predictions, we identified 114 proteins as putative SNED1 interactors, including the ECM protein fibronectin. Pathway analysis of the predicted SNED1 interactome further revealed that it may contribute to signaling through cell surface receptors, such as integrins, and participate in the regulation of ECM organization and developmental processes. Last, using fluorescence microscopy, we showed that SNED1 forms microfibrils within the ECM and partially colocalizes with fibronectin. Altogether, we provide a wealth of information on an understudied yet important ECM protein with the potential to decipher its pathophysiological functions.*

**Insights into the roles of charged residues in substrate binding and mode of action of mannuronan C-5 epimerase AlgE4**. Gaardløs M, Samsonov SA, Sletmoen M, Hjørnevik M, Sætrom GI, Tøndervik A, Aachmann FL. Glycobiology. 2021 Apr 1:cwab025. doi: 10.1093/glycob/cwab025.
**Corresponding authors**: sergey.samsonov@ug.edu.pl and finn.l.aachmann@ntnu.no
**Abstract**: *Mannuronan C-5 epimerases catalyse the epimerization of monomer residues in the polysaccharide alginate, changing the physical properties of the biopolymer. The enzymes are utilized to tailor alginate to numerous biological functions by alginate-producing organisms. The underlying molecular mechanisms that control the processive movement of the epimerase along the substrate chain is still elusive. To study this, we have used an interdisciplinary approach combining molecular dynamics simulations with experimental methods from mutant studies of AlgE4, where initial epimerase activity and product formation were addressed with NMR spectroscopy, and characteristics of enzyme-substrate interactions were obtained with isothermal titration calorimetry and optical tweezers. Positive charges lining the substrate-binding groove of AlgE4 appear to control the initial binding of poly-mannuronate, and binding also seems to be mediated by both electrostatic and hydrophobic interactions. After the catalytic reaction, negatively charged enzyme residues might facilitate dissociation of alginate from the positive residues, working like electrostatic switches, allowing the substrate to translocate in the binding groove. Molecular simulations show translocation increments of two monosaccharide units before the next productive binding event resulting in MG-block formation, with the epimerase moving with its N-terminus towards the reducing end of the alginate chain. Our results indicate that the charge pair R343-D345 might be directly involved in conformational changes of a loop that can be important for binding and dissociation. The computational and experimental approaches used in this study complement each other, allowing for a better understanding of individual residues' roles in binding and movement along the alginate chains.*

**Hair Histology and Glycosaminoglycans Distribution Probed by Infrared Spectral Imaging: Focus on Heparan Sulfate Proteoglycan and Glypican-1 during Hair Growth Cycle.** Colin-Pierre C, Untereiner V, Sockalingum GD, Berthélémy N, Danoux L, Bardey V, Mine S, Jeanmaire C, Ramont L, Brézillon S. Biomolecules. 2021 Jan 30;11(2):192. doi: 10.3390/biom11020192.

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**Abstract:** *The expression of glypicans in different hair follicle (HF) compartments and their potential roles during hair shaft growth are still poorly understood. Heparan sulfate proteoglycan (HSPG) distribution in HFs is classically investigated by conventional histology, biochemical analysis, and immunohistochemistry. In this report, a novel approach is proposed to assess hair histology and HSPG distribution changes in HFs at different phases of the hair growth cycle using infrared spectral imaging (IRSI). The distribution of HSPGs in HFs was probed by IRSI using the absorption region relevant to sulfation as a spectral marker. The findings were supported by Western immunoblotting and immunohistochemistry assays focusing on the glypican-1 expression and distribution in HFs. This study demonstrates the capacity of IRSI to identify the different HF tissue structures and to highlight protein, proteoglycan (PG), glycosaminoglycan (GAG), and sulfated GAG distribution in these structures. The comparison between anagen, catagen, and telogen phases shows the qualitative and/or quantitative evolution of GAGs as supported by Western immunoblotting. Thus, IRSI can simultaneously reveal the location of proteins, PGs, GAGs, and sulfated GAGs in HFs in a reagent- and label-free manner. From a dermatological point of view, IRSI shows its potential as a promising technique to study alopecia.*

**A guide to the composition and functions of the extracellular matrix.** Karamanos NK, Theocharis AD, Piperigkou Z, Manou D, Passi A, Skandalis SS, Vynios DH, Orian-Rousseau V, Ricard-Blum S, Schmelzer CEH, Duca L, Durbee M, Afratis NA, Troeberg L, Franchi M, Masola V, Onisto M. FEBS J 2021 Feb 19. doi: 10.1111/febs.15776. Online ahead of print.

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**Abstract:** *Extracellular matrix (ECM) is a dynamic 3-dimensional network of macromolecules that provides structural support for the cells and tissues. Accumulated knowledge clearly demonstrated over the last decade that ECM plays key regulatory roles since it orchestrates cell signaling, functions, properties and morphology. Extracellularly secreted as well as cell-bound factors are among the major members of the ECM family. Proteins/glycoproteins, such as collagens, elastin, laminins and tenascins, proteoglycans and glycosaminoglycans, hyaluronan, and their cell receptors such as CD44 and integrins, responsible for cell adhesion, comprise a well-organized functional network with significant roles in health and disease. On the other hand, enzymes such as matrix metalloproteinases and specific glycosidases including heparanase and hyaluronidases contribute to matrix remodeling and affect human health. Several cell processes and functions, among them cell proliferation and survival, migration, differentiation, autophagy, angiogenesis, and immunity regulation are affected by certain matrix components. Structural alterations have been also well associated with disease progression. This guide on the composition and functions of the ECM gives a broad overview of the matrisome, the major ECM macromolecules, and their interaction networks within the ECM and with the cell surface, summarizes their main structural features and their roles in tissue organization and cell functions, and emphasizes the importance of specific ECM constituents in disease development and progression as well as the advances in molecular targeting of ECM to design new therapeutic strategies.*

**Syndecan receptors: pericellular regulators in development and inflammatory disease.** Gopal S, Arokiasamy S, Pataki C, Whiteford JR, Couchman JR. Open Biol. 2021 Feb;11(2):200377. doi: 10.1098/rsob.200377.

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**Abstract**: *The syndecans are the major family of transmembrane proteoglycans, usually bearing multiple heparan sulfate chains. They are present on virtually all nucleated cells of vertebrates and are also present in invertebrates,*

*indicative of a long evolutionary history. Genetic models in both vertebrates and invertebrates have shown that syndecans link to the actin cytoskeleton and can fine-tune cell adhesion, migration, junction formation, polarity and differentiation. Although often associated as co-receptors with other classes of receptors (e.g. integrins, growth factor and morphogen receptors), syndecans can nonetheless signal to the cytoplasm in discrete ways. Syndecan expression levels are upregulated in development, tissue repair and an array of human diseases, which has led to the increased appreciation that they may be important in pathogenesis not only as diagnostic or prognostic agents, but also as potential targets. Here, their functions in development and inflammatory diseases are summarized, including their potential roles as conduits for viral pathogen entry into cells.*

**Novel human tenascin-C function-blocking camel single domain nanobodies**. Dhaouadi S, Benabderrazek R[¥], Loustau T[¥], Abou-Faycal C[¥], Ksouri A[¥], Erne W[¥], Murdamoothoo D, Mörgelin M, Kungl A, Jung A, Ledrappier S, Benlasfar Z, Bichet S, Chiquet-Ehrismann R[†], Hendaoui I, Orend G, Bouhaouala-Zahar B. Front Immunol, Special issue on "Tenascins: Key Players in Tissue Homeostasis and Defense", guest editors, K. Midwood, G. Orend, K. Imanaka-Yoshida, 2021; 12: 635166, doi:10.3389/ fimmu.2021. 635166, [¥] equal contribution
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**Abstract**: *The extracellular matrix (ECM) molecule Tenascin-C (TNC) is well-known to promote tumor progression by multiple mechanisms. However, reliable TNC detection in tissues of tumor banks remains limited. Therefore, we generated dromedary single-domain nanobodies Nb3 and Nb4 highly specific for human TNC (hTNC) and characterized the interaction with TNC by several approaches including ELISA, western blot, isothermal fluorescence titration and negative electron microscopic imaging. Our results revealed binding of both nanobodies to distinct sequences within fibronectin type III repeats of hTNC. By immunofluroescence and immunohistochemical imaging we observed that both nanobodies detected TNC expression in PFA and paraffin embedded human tissue from ulcerative colitis, solid tumors and liver metastasis. As TNC impairs cell adhesion to fibronectin we determined whether the nanobodies abolished this TNC function. Indeed, Nb3 and Nb4 restored adhesion of tumor and mesangial cells on a fibronectin/TNC substratum. We recently showed that TNC orchestrates the immune-suppressive tumor microenvironment involving chemoretention, causing tethering of CD11c+ myeloid/dendritic cells in the stroma. Here, we document that immobilization of DC2.4 dendritic cells by a CCL21 adsorbed TNC substratum was blocked by both nanobodies. Altogether, our novel TNC specific nanobodies could offer valuable tools for detection of TNC in the clinical practice and may be useful to inhibit the immune-suppressive and other functions of TNC in cancer and other diseases.*

**Tenascin-C Deficiency Is Associated With Reduced Bacterial Outgrowth During Klebsiella pneumoniae-Evoked Pneumosepsis in Mice.** Meijer MT, de Vos AF, Scicluna BP, Roelofs JL, Abou Fayçal C, Orend G, Uhel F, van der Poll T, 2021. Front Immunol, Special issue on "Tenascins: Key Players in Tissue Homeostasis and Defense", guest editors, K. Midwood, G. Orend, K. Imanaka-Yoshida, Front. Immunol., 11 March 2021, doi: 10.3389/fimmu.2021.600979.
**Corresponding author**: m.t.meijer@amsterdamumc.nl
**Abstract**: *Tenascin C (TNC) is an extracellular matrix glycoprotein that recently emerged as an immunomodulator. TNC-deficient (TNC−/−) mice were reported to have a reduced inflammatory response upon systemic administration of lipopolysaccharide, the toxic component of gram-negative bacteria. Here, we investigated the role of TNC during gram-negative pneumonia derived sepsis. TNC+/+ and TNC−/− mice were infected with Klebsiella pneumoniae via the airways and sacrificed 24 and 42 h thereafter for further analysis. Pulmonary TNC protein levels were elevated 42 h after infection in TNC+/+ mice and remained undetectable in TNC−/− mice. TNC−/− mice showed modestly lower bacterial loads in lungs and blood, and a somewhat reduced local—but not systemic—inflammatory response. Moreover, TNC−/− and TNC+/+ mice did not differ with regard to neutrophil recruitment, lung pathology or plasma markers of distal organ injury. These results suggest that while TNC shapes*

*the immune response during lipopolysaccharide-induced inflammation, this role may be superseded during pneumosepsis caused by a common gram-negative pathogen.*

**Did Tenascin-C Co-Evolve With the General Immune System of Vertebrates?** Orend G, Tucker RP. Front Immunol, Special issue "Tenascins: Key Players in Tissue Homeostasis and Defense", guest editors, K. Midwood, G. Orend, K. Imanaka-Yoshida. 2021 12:663902. doi: 10.3389/fimmu.2021.663902
**Corresponding author:** rptucker@ucdavis.edu
**Abstract:** *Tenascin-C plays important roles in immunity. Toll-like receptor 4, integrin α9β1 and chemokines have already been identified as key players in executing the immune regulatory functions of tenascin-C. Tenascin-C is also found in reticular fibers in lymphoid tissues, which are major sites involved in the regulation of adaptive immunity. Did the "tool box" for reading and interpreting the immune-regulating instructions imposed by tenascins and tenascin-C co-evolve? Though the extracellular matrix is ancient, tenascins evolved relatively recently. Tenascin-like genes are first encountered in cephalochordates and urochordates, which are widely accepted as the early branching chordate lineages. Vertebrates lacking jaws like the lamprey have tenascins, but a tenascin gene that clusters in the tenascin-C clade first appears in cartilaginous fish. Adaptive immunity apparently evolved independently in jawless and jawed vertebrates, with the former using variable lymphocyte receptors for antigen recognition, and the latter using immunoglobulins. Thus, while tenascins predate the appearance of adaptive immunity, the first tenascin-C appears to have evolved in the first organisms with immunoglobulin-based adaptive immunity. While a C-X-C chemokine is present in the lamprey, C-C chemokines also appear in the first organisms with immunoglobulin-based adaptive immunity, as does the major histocompatibility complex, T-cell receptors, Toll-like receptor 4 and integrin α9β1. Given the importance of tenascin-C in inflammatory events, the co-evolution of tenascin-C and key elements of adaptive and innate immunity is suggestive of a fundamental role for this extracellular matrix glycoprotein in the immune response of jawed vertebrates.*

**Tenascin-C immobilizes infiltrating T lymphocytes through CXCL12 promoting breast cancer progression.** Murdamoothoo D*, Sun Z*, Yilmaz A*, Deligne C, Velazquez-Quesada I, Erne W, M. Nascimento, Mörgelin M, Cremel G, Paul N, Carapito R, Abou-Faycal C, Midwood K, Loustau T, Orend G. EMBO Mol Med*, accepted,* * equal contribution.
**Corresponding author**: gertraud.orend@inserm.fr
**Abstract**: *Immune checkpoint therapy, where CD8 tumor infiltrating T lymphocytes (TIL) are reactivated, is a promising anti-cancer treatment approach, yet with low response rates. The extracellular matrix, in particular tenascin-C, may generate barriers for TIL. To investigate this possibility, we used a MMTV-NeuNT and syngeneic mammary gland grafting model derived thereof with engineered tenascin-C levels, and observed accumulation of CD8 TIL in tenascin-C-rich stroma. Inhibition studies revealed that tenascin-C induced CXCL12 through TLR4. By binding CXCL12 tenascin-C retained CD8 TIL in the stroma. Blockade of CXCR4, the receptor of CXCL12, enhanced macrophage and CD8 TIL infiltration, and reduced tumor growth and metastasis. Retention of CD8 TIL by tenascin-C/CXCL12 was also observed in human breast cancer by tissue staining. Moreover, high CD8 TIL numbers correlated with longer metastasis-free survival, unless tenascin-C and CXCL12 levels were also high representing the worsened condition. Altogether, these results may be useful for improving tumor immunity as diagnostic tool and for targeting tumor matrix to implement a future "TILmatrix-release-and-reactivate" strategy.*

**Fibronectin adsorption on oxygen plasma-treated polyurethane surfaces modulates endothelial cell response.** Daum R, Mrsic I, Hutterer J, Junginger A, Hinderer S, Meixner AJ, Gauglitz G, Chassé T, Schenke-Layland K. J Mater Chem B. 2021 Feb 14;9(6):1647-1660. doi: 10.1039/d0tb02757j.
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**Abstract***: Fibronectin coating increases implant biocompatibility by enhancing surface endothelialization via integrin-mediated binding. Surface properties determine the fibronectin orientation and conformation, dictating which ligands are presented, and therefore altering the bioactivity of an implant surface. In this study, polyurethane was treated with oxygen plasma, which allowed for a simultaneous modification of the surface chemistry and topography to modulate fibronectin adsorption. By varying the parameters of the treatment, human plasma fibronectin adsorbed on the surfaces in different conformations, orientations, and binding affinities, which was investigated by atomic force microscopy, fluorescence microscopy, monoclonal and polyclonal antibody staining and reflectometric interference spectroscopy. Apart from the most hydrophilic rough surfaces, the adsorbed fibronectin showed a lower binding affinity and less conformational change on the more hydrophilic surfaces. A large amount of exposed fibronectin-cell binding was detected on the rough treated and the smooth untreated surfaces. Primary isolated human umbilical vein and human microvascular endothelial cells showed a significantly higher cell adherence on the absorbed fibronectin with a low binding affinity and low conformational changes. Significant differences in the formation of mature focal adhesions and the reorganization of F-actin were identified on the rough treated and the smooth untreated surfaces. Our data suggest that oxygen plasma treatment is a reliable technique for the modulation of fibronectin adsorption in order to adjust fibronectin bioactivity and impact cell responses to implant surfaces.*

**Regulation of the Wound Healing Response during Aging.** Ding X, Kakanj P, Leptin M, Eming SA. J Invest Dermatol. 2021 Apr;141(4S):1063-1070. doi: 10.1016/j.jid.2020.11.014.
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**Abstract:** *An effective healing response is critical to promote and ensure healthy aging. Major discoveries in both fields-repair and aging-have led to a better understanding of the mechanisms regulating the healing response and of the complexity of the aging process. It will now be important to translate and connect those findings to improve our insights into the decline of regeneration in the elderly. Furthermore, we need to understand how this process can be stalled to maintain and promote tissue resilience. Furthermore, it remains to be explored how the findings in model organisms are conserved in human wounds and how these findings might be translated into the clinic.*

**Quantitative single-protein imaging reveals molecular complex formation of integrin, talin, and kindlin during cell adhesion.** Fischer LS, Klingner C, Schlichthaerle T, Strauss MT, Böttcher R, Fässler R, Jungmann R, Grashoff C. Nat Commun. 2021 Feb 10;12(1):919. doi: 10.1038/s41467-021-21142-2.
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**Abstract:** *Single-molecule localization microscopy (SMLM) enabling the investigation of individual proteins on molecular scales has revolutionized how biological processes are analysed in cells. However, a major limitation of imaging techniques reaching single-protein resolution is the incomplete and often unknown labeling and detection efficiency of the utilized molecular probes. As a result, fundamental processes such as complex formation of distinct molecular species cannot be reliably quantified. Here, we establish a super-resolution microscopy framework, called quantitative single-molecule colocalization analysis (qSMCL), which permits the identification of absolute molecular quantities and thus the investigation of molecular-scale processes inside cells. The method combines multiplexed single-protein resolution imaging, automated cluster detection, in silico data simulation procedures, and widely applicable experimental controls to determine absolute fractions and spatial coordinates of interacting species on a true molecular level, even in highly crowded subcellular structures. The first application of this framework allowed the identification of a long-sought ternary adhesion complex-consisting of talin, kindlin and active β1-integrin-that specifically forms in cell-matrix adhesion sites. Together, the experiments demonstrate that qSMCL allows an absolute quantification of multiplexed SMLM data and thus should be useful for investigating molecular mechanisms underlying numerous processes in cells.*

**A new MMP-mediated prodomain cleavage mechanism to activate bone morphogenetic proteins from the extracellular matrix.** Furlan AG, Spanou CES, Godwin ARF, Wohl AP, Zimmermann LA, Imhof T, Koch M, Baldock C, Sengle G. FASEB J. 2021 Mar;35(3):e21353. doi: 10.1096/fj.202001264R.
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**Abstract:** *Since their discovery as pluripotent cytokines extractable from bone matrix, it has been speculated how bone morphogenetic proteins (BMPs) become released and activated from the extracellular matrix (ECM). In contrast to TGF-βs, most investigated BMPs are secreted as bioactive prodomain (PD)-growth factor (GF) complexes (CPLXs). Recently, we demonstrated that PD-dependent targeting of BMP-7 CPLXs to the extracellular fibrillin microfibril (FMF) components fibrillin-1 and -2 represents a BMP sequestration mechanism by rendering the GF latent. Understanding how BMPs become activated from ECM scaffolds such as FMF is crucial to elucidate pathomechanisms characterized by aberrant BMP activation and ECM destruction. Here, we describe a new MMP-dependent BMP-7 activation mechanism from ECM-targeted pools via specific PD degradation. Using Edman sequencing and mutagenesis, we identified a new and conserved MMP-13 cleavage site within the BMP-7 PD. A degradation screen with different BMP family PDs and representative MMP family members suggested utilization of the identified site in a general MMP-driven BMP activation mechanism. Furthermore, sandwich ELISA and solid phase cleavage studies in combination with bioactivity assays, single particle TEM, and in silico molecular docking experiments provided evidence that PD cleavage by MMP-13 leads to BMP-7 CPLX disintegration and bioactive GF release.*

**Fueling Cell Invasion through Extracellular Matrix.** Garde A, Sherwood DR**.** Trends Cell Biol. 2021 Feb 3:S0962-8924(21)00010-6. doi: 10.1016/j.tcb.2021.01.006.
**Corresponding author:** david.sherwood@duke.edu
**Abstract:** *Cell invasion through extracellular matrix (ECM) has pivotal roles in cell dispersal during development, immune cell trafficking, and cancer metastasis. Many elegant studies have revealed the specialized cellular protrusions, proteases, and distinct modes of migration invasive cells use to overcome ECM barriers. Less clear, however, is how invasive cells provide energy, specifically ATP, to power the energetically demanding membrane trafficking, F-actin polymerization, and actomyosin machinery that mediate break down, remodeling, and movement through ECMs. Here, we provide an overview of the challenges of examining ATP generation and delivery within invading cells and how recent studies using diverse invasion models, experimental approaches, and energy biosensors are revealing that energy metabolism is an integral component of cell invasive behavior that is dynamically tuned to overcome the ECM environment.*

**Prognostic impact of the glypican family of heparan sulfate proteoglycans on the survival of breast cancer patients.** Grillo PK, Győrffy B, Götte M. J Cancer Res Clin Oncol. 2021 Mar 19. doi: 10.1007/s00432-021-03597-4.
**Corresponding author:** martingotte@uni-muenster.de
**Abstract:** *Purpose: Dysregulated expression of proteoglycans influences the outcome and progression of numerous cancers. Several studies have investigated the role of individual glypicans in cancer, however, the impact of the whole glypican family of heparan sulfate proteoglycans on prognosis of a large patient cohort of breast cancer patients has not yet been investigated. In the present study, our aim was to investigate the prognostic power of the glypicans in breast cancer patients. Methods: We used a public database including both gene expression data and survival information for 3951 breast cancer patients to determine the prognostic value of glypicans on relapse-free survival using Cox regression analysis. Moreover, we performed quantitative Real-Time PCR to determine glypican gene expression levels in seven representative breast cancer cell lines. Results: We found that high GPC3 levels were associated with a better prognosis in overall breast cancer patients. When stratified by hormone receptor status, we found that in worse prognosis subtypes low GPC1 levels correlate with a longer relapse-free survival, and in more favorable subtypes low GPC6 was associated with longer survival.*

*Conclusion: Our study concludes that glypicans could act as subtype-specific biomarkers for the prognosis of breast cancer patients and sparks hope for future research on glypicans possibly eventually providing targets for the treatment of the disease.*

**Cell-surface heparan sulfate proteoglycans as multifunctional integrators of signaling in cancer.** Hassan N, Greve B, Espinoza-Sánchez NA, Götte M. Cell Signal. 2021 Jan;77:109822. doi: 10.1016/j.cellsig.2020.109822.
**Corresponding author:** latmw_yo@hotmail.com and martingotte@uni-muenster.de
**Abstract:** *Proteoglycans (PGs) represent a large proportion of the components that constitute the extracellular matrix (ECM). They are a diverse group of glycoproteins characterized by a covalent link to a specific glycosaminoglycan type. As part of the ECM, heparan sulfate (HS)PGs participate in both physiological and pathological processes including cell recruitment during inflammation and the promotion of cell proliferation, adhesion and motility during development, angiogenesis, wound repair and tumor progression. A key function of HSPGs is their ability to modulate the expression and function of cytokines, chemokines, growth factors, morphogens, and adhesion molecules. This is due to their capacity to act as ligands or co-receptors for various signal-transducing receptors, affecting pathways such as FGF, VEGF, chemokines, integrins, Wnt, notch, IL-6/JAK-STAT3, and NF-κB. The activation of those pathways has been implicated in the induction, progression, and malignancy of a tumor. For many years, the study of signaling has allowed for designing specific drugs targeting these pathways for cancer treatment, with very positive results. Likewise, HSPGs have become the subject of cancer research and are increasingly recognized as important therapeutic targets. Although they have been studied in a variety of preclinical and experimental models, their mechanism of action in malignancy still needs to be more clearly defined. In this review, we discuss the role of cell-surface HSPGs as pleiotropic modulators of signaling in cancer and identify them as promising markers and targets for cancer treatment.*

**The Burden of Post-Translational Modification (PTM)-Disrupting Mutations in the Tumor Matrisome.** Holstein E, Dittmann A, Kääriäinen A, Pesola V, Koivunen J, Pihlajaniemi T, Naba A, Izzi V. Cancers (Basel). 2021 Mar 3;13(5):1081. doi: 10.3390/cancers13051081.
**Corresponding author:** valerio.izzi@oulu.fi
**Abstract:** *Background: To evaluate the occurrence of mutations affecting post-translational modification (PTM) sites in matrisome genes across different tumor types, in light of their genomic and functional contexts and in comparison with the rest of the genome. Methods: This study spans 9075 tumor samples and 32 tumor types from The Cancer Genome Atlas (TCGA) Pan-Cancer cohort and identifies 151,088 non-silent mutations in the coding regions of the matrisome, of which 1811 affecting known sites of hydroxylation, phosphorylation, N- and O-glycosylation, acetylation, ubiquitylation, sumoylation and methylation PTM. Results: PTM-disruptive mutations (PTMmut) in the matrisome are less frequent than in the rest of the genome, seem independent of cell-of-origin patterns but show dependence on the nature of the matrisome protein affected and the background PTM types it generally harbors. Also, matrisome PTMmut are often found among structural and functional protein regions and in proteins involved in homo- and heterotypic interactions, suggesting potential disruption of matrisome functions. Conclusions: Though quantitatively minoritarian in the spectrum of matrisome mutations, PTMmut show distinctive features and damaging potential which might concur to deregulated structural, functional, and signaling networks in the tumor microenvironment.*

**Pivotal Role of Tenascin-W (-N) in Postnatal Incisor Growth and Periodontal Ligament Remodeling.** Imhof T, Balic A, Heilig J, Chiquet-Ehrismann R, Chiquet M, Niehoff A, Brachvogel B, Thesleff I, Koch M. Front Immunol. 2021 Jan 22;11:608223. doi: 10.3389/fimmu.2020.608223.
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**Abstract:** *The continuously growing mouse incisor provides a fascinating model for studying stem cell regulation and organ renewal. In the incisor, epithelial and mesenchymal stem cells assure lifelong tooth growth. The epithelial stem cells reside in a niche known as the cervical loop. Mesenchymal stem cells are located in the nearby apical neurovascular bundle and in the neural plexus. So far, little is known about extracellular cues that are controlling incisor stem cell renewal and guidance. The extracellular matrix protein tenascin-W, also known as tenascin-N (TNN), is expressed in the mesenchyme of the pulp and of the periodontal ligament of the incisor, and is closely associated with collagen 3 fibers. Here, we report for the first time the phenotype of tenascin-W/TNN deficient mice, which in a C57BL/6N background exhibit a reduced body weight and lifespan. We found major defects in the alveolar bone and periodontal ligament of the growing rodent incisors, whereas molars were not affected. The alveolar bone around the incisor was replaced by a dense scar-like connective tissue, enriched with newly formed nerve fibers likely leading to periodontal pain, less food intake and reduced body weight. Using soft food to reduce mechanical load on the incisor partially rescued the phenotype. In situ hybridization and Gli1 reporter mouse experiments revealed decreased hedgehog signaling in the incisor mesenchymal stem cell compartment, which coordinates the development of mesenchymal stem cell niche. These results indicate that TNN deficiency in mice affects periodontal remodeling and increases nerve fiber branching. Through periodontal pain the food intake is reduced and the incisor renewal and the neurovascular sonic hedgehog secretion rate are reduced. In conclusion, tenascin-W/TNN seems to have a primary function in rapid periodontal tissue remodeling and a secondary function in mechanosensation.*

**COMP and TSP-4: Functional Roles in Articular Cartilage and Relevance in Osteoarthritis.** Maly K, Andres Sastre E, Farrell E, Meurer A, Zaucke F. Int J Mol Sci. 2021 Feb 24;22(5):2242. doi: 10.3390/ijms22052242.

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**Abstract:** *Osteoarthritis (OA) is a slow-progressing joint disease, leading to the degradation and remodeling of the cartilage extracellular matrix (ECM). The usually quiescent chondrocytes become reactivated and accumulate in cell clusters, become hypertrophic, and intensively produce not only degrading enzymes, but also ECM proteins, like the cartilage oligomeric matrix protein (COMP) and thrombospondin-4 (TSP-4). To date, the functional roles of these newly synthesized proteins in articular cartilage are still elusive. Therefore, we analyzed the involvement of both proteins in OA specific processes in in vitro studies, using porcine chondrocytes, isolated from femoral condyles. The effect of COMP and TSP-4 on chondrocyte migration was investigated in transwell assays and their potential to modulate the chondrocyte phenotype, protein synthesis and matrix formation by immunofluorescence staining and immunoblot. Our results demonstrate that COMP could attract chondrocytes and may contribute to a repopulation of damaged cartilage areas, while TSP-4 did not affect this process. In contrast, both proteins similarly promoted the synthesis and matrix formation of collagen II, IX, XII and proteoglycans, but inhibited that of collagen I and X, resulting in a stabilized chondrocyte phenotype. These data suggest that COMP and TSP-4 activate mechanisms to protect and repair the ECM in articular cartilage.*

**C-Terminal Peptide Modifications Reveal Direct and Indirect Roles of Hedgehog Morphogen Cholesteroylation.** Manikowski D, Kastl P, Schürmann S, Ehring K, Steffes G, Jakobs P, Grobe K. Front Cell Dev Biol. 2021 Jan 12;8:615698. doi: 10.3389/fcell.2020.615698.

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**Abstract:** *Hedgehog (Hh) morphogens are involved in embryonic development and stem cell biology and, if misregulated, can contribute to cancer. One important post-translational modification with profound impact on Hh biofunction is its C-terminal cholesteroylation during biosynthesis. The current hypothesis is that the cholesterol moiety is a decisive factor in Hh association with the outer plasma membrane leaflet of producing cells, cell-surface Hh multimerization, and its transport and signaling. Yet, it is not decided whether the cholesterol moiety is directly involved in all of these processes, because their functional interdependency raises the alternative possibility that the cholesterol initiates early processes directly and that these processes can then steer later stages*

*of Hh signaling independent of the lipid. We generated variants of the C-terminal Hh peptide and observed that these cholesteroylated peptides variably impaired several post-translational processes in producing cells and Hh biofunction in Drosophila melanogaster eye and wing development. We also found that substantial Hh amounts separated from cholesteroylated peptide tags in vitro and in vivo and that tagged and untagged Hh variants lacking their C-cholesterol moieties remained bioactive. Our approach thus confirms that Hh cholesteroylation is essential during the early steps of Hh production and maturation but also suggests that it is dispensable for Hh signal reception at receiving cells.*

**Integrative analysis of cell state changes in lung fibrosis with peripheral protein biomarkers.** Mayr CH, Simon LM, Leuschner G, Ansari M, Schniering J, Geyer PE, Angelidis I, Strunz M, Singh P, Kneidinger N, Reichenberger F, Silbernagel E, Böhm S, Adler H, Lindner M, Maurer B, Hilgendorff A, Prasse A, Behr J, Mann M, Eickelberg O, Theis FJ, Schiller HB. EMBO Mol Med. 2021 Apr 9;13(4):e12871. doi: 10.15252/emmm.202012871.
**Corresponding author:** fabian.theis@helmholtz-muenchen.de and herbert.schiller@helmholtz-muenchen.de
**Abstract:** *The correspondence of cell state changes in diseased organs to peripheral protein signatures is currently unknown. Here, we generated and integrated single-cell transcriptomic and proteomic data from multiple large pulmonary fibrosis patient cohorts. Integration of 233,638 single-cell transcriptomes (n = 61) across three independent cohorts enabled us to derive shifts in cell type proportions and a robust core set of genes altered in lung fibrosis for 45 cell types. Mass spectrometry analysis of lung lavage fluid (n = 124) and plasma (n = 141) proteomes identified distinct protein signatures correlated with diagnosis, lung function, and injury status. A novel SSTR2+ pericyte state correlated with disease severity and was reflected in lavage fluid by increased levels of the complement regulatory factor CFHR1. We further discovered CRTAC1 as a biomarker of alveolar type-2 epithelial cell health status in lavage fluid and plasma. Using cross-modal analysis and machine learning, we identified the cellular source of biomarkers and demonstrated that information transfer between modalities correctly predicts disease status, suggesting feasibility of clinical cell state monitoring through longitudinal sampling of body fluid proteomes.*

**Expression and Localization of Thrombospondins, Plastin 3, and STIM1 in Different Cartilage Compartments of the Osteoarthritic Varus Knee.** Mählich D, Glasmacher A, Müller I, Oppermann J, Grevenstein D, Eysel P, Heilig J, Wirth B, Zaucke F, Niehoff A. Int J Mol Sci. 2021 Mar 17;22(6):3073.
**Corresponding author:** niehoff@dshs-koeln.de
**Abstract:** *Osteoarthritis (OA) is a multifactorial disease which is characterized by a change in the homeostasis of the extracellular matrix (ECM). The ECM is essential for the function of the articular cartilage and plays an important role in cartilage mechanotransduction. To provide a better understanding of the interaction between the ECM and the actin cytoskeleton, we investigated the localization and expression of the Ca2+-dependent proteins cartilage oligomeric matrix protein (COMP), thrombospondin-1 (TSP-1), plastin 3 (PLS3) and stromal interaction molecule 1 (STIM1). We investigated 16 patients who suffered from varus knee OA and performed a topographical analysis of the cartilage from the medial and lateral compartment of the proximal tibial plateau. In a varus knee, OA is more pronounced in the medial compared to the lateral compartment as a result of an overloading due to the malalignment. We detected a location-dependent staining of PLS3 and STIM1 in the articular cartilage tissue. The staining intensity for both proteins correlated with the degree of cartilage degeneration. The staining intensity of TSP-1 was clearly reduced in the cartilage of the more affected medial compartment, an observation that was confirmed in cartilage extracts by immunoblotting. The total amount of COMP was unchanged; however, slight changes were detected in the localization of the protein. Our results provide novel information on alterations in OA cartilage suggesting that Ca2+-dependent mechanotransduction between the ECM and the actin cytoskeleton might play an essential role in the pathomechanism of OA.*

**Redox proteomics reveals an interdependence of redox modification and location of adhesome proteins in NGF-treated PC12 cells.** Meißner J, Rezaei M, Siepe I, Ackermann D, König S, Eble JA. Free Radic Biol Med. 2021 Feb 20;164:341-353. doi: 10.1016/j.freeradbiomed.2021.01.019.
**Corresponding author:** johannes.eble@uni-muenster.de
**Abstract:** *Proteomics studies have revealed that adhesomes are assembled from a plethora of proteins at integrin-mediated cellular contact sites with the extracellular matrix. By combining dimedone-trapping of sulfenylated proteins with the purification of the adhesome complex, we extended previous proteomics approaches on adhesomes to a redox proteomic analysis. This added a new aspect of adhesome complexity as individual adhesome proteins change their redox state in response to environmental signals. As model system, rat pheochromocytoma PC12 cells were studied in contact with type IV collagen and in response to nerve growth factor (NGF). NGF stimulates the endogenous production of reactive oxygen species (ROS) and the formation of neurite-like cell protrusions, which are anchored to the substratum via adhesomes. Dimedone detects the reversible oxidation of cysteine thiol groups into sulfenic acid groups which was used in proteomic analysis of adhesome proteins revealing that sulfenylation and location of proteins mutually influence each other. For some proteins, identified by the redox proteomics approach, among them Nck-associated protein-1 (Nap-1), proximity ligation analysis and co-immunoprecipitation assays proved that protein sulfenylation sites colocalize with adhesomes of protrusions. In conclusion, the suprastructural composition and function of adhesomes is redox-regulated by ROS. Of interest in this respect, isoform-selective pharmacological inhibition of NADPH-oxidases (Noxs) reduced the adhesomal location of the collagen-binding α1β1 integrin and the length of the outgrowing neurites, indicative of a role of Nox isoforms in the redox-regulation of adhesomes. Thus, our novel redox proteomics approach not only revealed redox-modifications and the potential redox-regulation of adhesomes and their constituents but it may also provide a tool to analyze the ROS-stimulated neurite repair of peripheral neurons.*

**Plants as source of new therapies for endometriosis: a review of preclinical and clinical studies.** Meresman GF, Götte M, Laschke MW. Hum Reprod Update. 2021 Feb 19;27(2):367-392. doi: 10.1093/humupd/dmaa039.
**Corresponding author:** martingotte@uni-muenster.de
**Abstract:** *Background: Given the disadvantages and limitations of current endometriosis therapy, there is a progressive increase in studies focusing on plant-derived agents as a natural treatment option with the intention of achieving high efficiency, avoiding adverse effects and preserving the chance for successful pregnancy. The heterogeneity of these studies in terms of evaluated agents, applied approaches and outcomes illustrates the need for an up-to-date summary and critical view on this rapidly growing field in endometriosis research. Objective and rationale: This review provides a comprehensive overview of plant-derived agents and natural treatment strategies that are under preclinical or clinical investigation and critically evaluates their potential for future endometriosis therapy. Search methods: An English language PubMed literature search was performed using variations of the terms 'endometriosis', 'natural therapy', 'herb/herbal', 'plant', 'flavonoid', 'polyphenol', 'phytochemical', 'bioactive', 'Kampo' and 'Chinese medicine'. It included both animal and human studies. Moreover, the Clinicaltrials.gov database was searched with the term 'endometriosis' for clinical trials on plant-derived agents. No restriction was set for the publication date. Outcomes: Natural therapies can be assigned to three categories: (i) herbal extracts, (ii) specific plant-derived bioactive compounds and (iii) Chinese herbal medicine (CHM). Agents of the first category have been shown to exert anti-proliferative, anti-inflammatory, anti-angiogenic and anti-oxidant effects on endometrial cells and endometriotic lesions. However, the existing evidence supporting their use in endometriosis therapy is quite limited. The most studied specific plant-derived bioactive compounds are resveratrol, epigallocatechin-3-gallate, curcumin, puerarin, ginsenosides, xanthohumol, 4-hydroxybenzyl alcohol, quercetin, apigenin, carnosic acid, rosmarinic acid, wogonin, baicalein, parthenolide, andrographolide and cannabinoids, with solid evidence about their inhibitory activity in experimental*

*endometriosis models. Their mechanisms of action include pleiotropic effects on known signalling effectors: oestrogen receptor-α, cyclooxygenase-2, interleukin-1 and -6, tumour necrosis factor-α, intercellular adhesion molecule-1, vascular endothelial growth factor, nuclear factor-kappa B, matrix metalloproteinases as well as reactive oxygen species (ROS) and apoptosis-related proteins. Numerous studies suggest that treatment with CHM is a good choice for endometriosis management. Even under clinical conditions, this approach has already been shown to decrease the size of endometriotic lesions, alleviate chronic pelvic pain and reduce postoperative recurrence rates. Wider implications: The necessity to manage endometriosis as a chronic disease highlights the importance of identifying novel and affordable long-term safety therapeutics. For this purpose, natural plant-derived agents represent promising candidates. Many of these agents exhibit a pleiotropic action profile, which simultaneously inhibits fundamental processes in the pathogenesis of endometriosis, such as proliferation, inflammation, ROS formation and angiogenesis. Hence, their inclusion into multimodal treatment concepts may essentially contribute to increase the therapeutic efficiency and reduce the side effects of future endometriosis therapy.*

**Syndecan-4 as a Pathogenesis Factor and Therapeutic Target in Cancer.** Onyeisi JOS, Lopes CC, Götte M. Biomolecules. 2021 Mar 26;11(4):503. doi: 10.3390/biom11040503.
**Corresponding author:** jessicaoyie@hotmail.com and martingotte@uni-muenster.de
**Abstract:** *Cancer is an important cause of morbidity and mortality worldwide. Advances in research on the biology of cancer revealed alterations in several key pathways underlying tumorigenesis and provided molecular targets for developing new and improved existing therapies. Syndecan-4, a transmembrane heparan sulfate proteoglycan, is a central mediator of cell adhesion, migration and proliferation. Although several studies have demonstrated important roles of syndecan-4 in cell behavior and its interactions with growth factors, extracellular matrix (ECM) molecules and cytoskeletal signaling proteins, less is known about its role and expression in multiple cancer. The data summarized in this review demonstrate that high expression of syndecan-4 is an unfavorable biomarker for estrogen receptor-negative breast cancer, glioma, liver cancer, melanoma, osteosarcoma, papillary thyroid carcinoma and testicular, kidney and bladder cancer. In contrast, in neuroblastoma and colorectal cancer, syndecan-4 is downregulated. Interestingly, syndecan-4 expression is modulated by anticancer drugs. It is upregulated upon treatment with zoledronate and this effect reduces invasion of breast cancer cells. In our recent work, we demonstrated that the syndecan-4 level was reduced after trastuzumab treatment. Similarly, syndecan-4 levels are also reduced after panitumumab treatment. Together, the data found suggest that syndecan-4 level is crucial for understanding the changes involving in malignant transformation, and also demonstrate that syndecan-4 emerges as an important target for cancer therapy and diagnosis.*

**Podoplanin is required for tumor cell invasion in cutaneous squamous cell carcinoma.** Schwab M, Lohr S, Schneider J, Kaiser M, Krunic D, Helbig D, Géraud C, Angel P. Exp Dermatol. 2021 Mar 30. doi: 10.1111/exd.14344.
**Corresponding author:** p.angel@dkfz.de
**Abstract:** *The invasiveness of late-stage cutaneous squamous cell carcinoma (cSCC) is associated with poor patients' prognosis and linked to strong upregulation of the glycoprotein Podoplanin (PDPN) in cancer cells. However, the function of PDPN in these processes in cSCC carcinogenesis has not been characterized in detail yet. Employing a CRISPR/Cas9-based loss-of-function approach on murine cSCC cells, we show that the loss of Pdpn results in decreased migration and invasion in vitro. Complementing these in vitro studies, labelled murine control and Pdpn knockout cells were injected orthotopically into the dermis of nude mice to recapitulate the formation of human cSCC displaying a well-differentiated morphology with a PDPN-positive reaction in fibroblasts in the tumor stroma. Smaller tumors were observed upon Pdpn loss, which is associated with reduced tumor cell infiltration into the stroma. Utilizing Pdpn mutants in functional experiments in vitro, we provide evidence that both the intra- and extracellular domains are essential for cancer cell invasion. These findings underline the critical*

*role of PDPN in cSCC progression and highlight potential therapeutic strategies targeting PDPN-dependent cancer cell invasion, especially in late-stage cSCC patients.*

**Adrenergic signalling in osteoarthritis.** Sohn R, Rösch G, Junker M, Meurer A, Zaucke F, Jenei-Lanzl Z. Cell Signal. 2021 Jun;82:109948. doi: 10.1016/j.cellsig.2021.109948.
**Corresponding author:** zsuzsa.jenei-lanzl@kgu.de
**Abstract***: Adrenoceptors (ARs) mediate the effects of the sympathetic neurotransmitters norepinephrine (NE) and epinephrine (E) in the human body and play a central role in physiologic and pathologic processes. Therefore, ARs have long been recognized as targets for therapeutic agents, especially in the field of cardiovascular medicine. During the past decades, the contribution of the sympathetic nervous system (SNS) and particularly of its major peripheral catecholamine NE to the pathogenesis of osteoarthritis (OA) attracted growing interest. OA is the most common degenerative joint disorder worldwide and a disease of the whole joint. It is characterized by progressive degradation of articular cartilage, synovial inflammation, osteophyte formation, and subchondral bone sclerosis mostly resulting in chronic pain. The subchondral bone marrow, the periosteum, the synovium, the vascular meniscus and numerous tendons and ligaments are innervated by tyrosine hydroxylase-positive (TH+) sympathetic nerve fibers that release NE into the synovial fluid and cells of all abovementioned joint tissues express at least one out of nine AR subtypes. During the past decades, several in vitro studies explored the AR-mediated effects of NE on different cell types in the joint. So far, only a few studies used animal OA models to investigate the contribution of distinct AR subtypes to OA pathogenesis in vivo. This narrative review shortly summarizes the current background knowledge about ARs and their signalling pathways at first. In the second part, we focus on recent findings in the field of NE-induced AR-mediated signalling in different joint tissues during OA pathogenesis and at the end, we will delineate the potential of targeting the adrenergic signalling for OA prevention or treatment. We used the PubMed bibliographic database to search for keywords such as 'joint' or 'cartilage' or 'synovium' or 'bone' and 'osteoarthritis' and/or 'trauma' and 'sympathetic nerve fibers' and/or 'norepinephrine' and 'adrenergic receptors / adrenoceptors' as well as 'adrenergic therapy'.*

**Collagen I triggers directional migration, invasion and matrix remodeling of stroma cells in a 3D spheroid model of endometriosis.** Stejskalová A, Fincke V, Nowak M, Schmidt Y, Borrmann K, von Wahlde MK, Schäfer SD, Kiesel L, Greve B, Götte M. Sci Rep. 2021 Feb 18;11(1):4115. doi: 10.1038/s41598-021-83645-8.
**Corresponding author:** martingotte@uni-muenster.de
**Abstract:** *Endometriosis is a painful gynecological condition characterized by ectopic growth of endometrial cells. Little is known about its pathogenesis, which is partially due to a lack of suitable experimental models. Here, we use endometrial stromal (St-T1b), primary endometriotic stromal, epithelial endometriotic (12Z) and co-culture (1:1 St-T1b:12Z) spheroids to mimic the architecture of endometrium, and either collagen I or Matrigel to model ectopic locations. Stromal spheroids, but not single cells, assumed coordinated directional migration followed by matrix remodeling of collagen I on day 5 or 7, resembling ectopic lesions. While generally a higher area fold increase of spheroids occurred on collagen I compared to Matrigel, directional migration was not observed in co-culture or in 12Z cells. The fold increase in area on collagen I was significantly reduced by MMP inhibition in stromal but not 12Z cells. Inhibiting ROCK signalling responsible for actomyosin contraction increased the fold increase of area and metabolic activity compared to untreated controls on Matrigel. The number of protrusions emanating from 12Z spheroids on Matrigel was decreased by microRNA miR-200b and increased by miR-145. This study demonstrates that spheroid assay is a promising pre-clinical tool that can be used to evaluate small molecule drugs and microRNA-based therapeutics for endometriosis.*

**Resident interstitial lung fibroblasts and their role in alveolar stem cell niche development, homeostasis, injury, and regeneration.** Ushakumary MG, Riccetti M, Perl AT. Stem Cells Transl Med. 2021 Feb 24. doi: 10.1002/sctm.20-0526.

**Corresponding author:** anne.perl@cchmc.org

**Abstract:** *Developing, regenerating, and repairing a lung all require interstitial resident fibroblasts (iReFs) to direct the behavior of the epithelial stem cell niche. During lung development, distal lung fibroblasts, in the form of matrix-, myo-, and lipofibroblasts, form the extra cellular matrix (ECM), create tensile strength, and support distal epithelial differentiation, respectively. During de novo septation in a murine pneumonectomy lung regeneration model, developmental processes are reactivated within the iReFs, indicating progenitor function well into adulthood. In contrast to the regenerative activation of fibroblasts upon acute injury, chronic injury results in fibrotic activation. In murine lung fibrosis models, fibroblasts can pathologically differentiate into lineages beyond their normal commitment during homeostasis. In lung injury, recently defined alveolar niche cells support the expansion of alveolar epithelial progenitors to regenerate the epithelium. In human fibrotic lung diseases like bronchopulmonary dysplasia (BPD), idiopathic pulmonary fibrosis (IPF), and chronic obstructive pulmonary disease (COPD), dynamic changes in matrix-, myo-, lipofibroblasts, and alveolar niche cells suggest differential requirements for injury pathogenesis and repair. In this review, we summarize the role of alveolar fibroblasts and their activation stage in alveolar septation and regeneration and incorporate them into the context of human lung disease, discussing fibroblast activation stages and how they contribute to BPD, IPF, and COPD.*

**Transgenic inhibition of interleukin-6 trans-signaling does not prevent skeletal pathologies in mucolipidosis type II mice.** Westermann LM, Baranowsky A, Di Lorenzo G, Danyukova T, Soul J, Schwartz JM, Hendrickx G, Amling M, Rose-John S, Garbers C, Schinke T, Pohl S. Sci Rep. 2021 Feb 11;11(1):3556. doi: 10.1038/s41598-021-82802-3.

**Corresponding author:** s.pohl@uke.de

**Abstract:** *Severe skeletal alterations are common symptoms in patients with mucolipidosis type II (MLII), a rare lysosomal storage disorder of childhood. We have previously reported that progressive bone loss in a mouse model for MLII is caused by an increased number of bone-resorbing osteoclasts, which is accompanied by elevated expression of the cytokine interleukin-6 (IL-6) in the bone microenvironment. In the present study we addressed the question, if pharmacological blockade of IL-6 can prevent the low bone mass phenotype of MLII mice. Since the cellular IL-6 response can be mediated by either the membrane-bound (classic signaling) or the soluble IL-6 receptor (trans-signaling), we first performed cell culture assays and found that both pathways can increase osteoclastogenesis. We then crossed MLII mice with transgenic mice expressing the recombinant soluble fusion protein sgp130Fc, which represents a natural inhibitor of IL-6 trans-signaling. By undecalcified histology and bone-specific histomorphometry we found that high circulating sgp130Fc levels do not affect skeletal growth or remodeling in wild-type mice. Most importantly, blockade of IL-6 trans-signaling did neither reduce osteoclastogenesis, nor increase bone mass in MLII mice. Therefore, our data clearly demonstrate that the bone phenotype of MLII mice cannot be corrected by blocking the IL-6 trans-signaling.*

## International travel grants

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

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

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

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

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

## Meeting announcements

### The French & German Societies for Matrix Biology organise a joint online scientific meeting free of charge from May 26 to May 28, 2021

Numerous opportunities for scientists, early career researchers and PhD students to present their work!


**Registration and additional information on the meeting website.**
http://matrixbiology2021.univ-lyon1.fr/

# MATRIX BIOLOGY EUROPE 2020

## Dick Heinegård Award Session

**2:00 PM - May 31st, 2021** (Central European Summer Time)

**Join Zoom Meeting**

https://us02web.zoom.us/j/84392248916?pwd=bVhmYmRKamEzcTVaK0lTU0pOQU8wdz09

ID meeting: 843 9224 8916 Passcode: 784419

| | |
|---|---|
| **11** | Session welcome<br>**Alberto Passi** |
| **14:05 – 14:30** | Invited Speaker Lecture<br>**Nikos Karamanos (Greece)** TBA |
| | **DICK HEINEGARD CANDIDATE PRESENTATIONS** |
| **14:35 – 14:45** | **Samantha Arokiasamy (United Kingdom)**<br>Identification of a novel Syndecan 3-based therapeutic to inhibit pathological neovascularization |
| **14:50 – 15:00** | **Kalle Sipila (Finland)**<br>Embigin is a novel fibronectin receptor that regulates the homeostasis of sebocyte progenitors |
| **15:05 - 15:15** | **Cherine Abou-Faycal (France)**<br>Role of Tenascin-C in ANCA-associated vasculitis |
| **15:20 – 15:30** | **Jana Riegger (Germany)**<br>Pharmacological Modulation of Posttraumatic Matrix Degradation and Regeneration in Articular Cartilage |
| **15:35 – 15:45** | **Arlyng Gonzalez-Vazquez (Ireland)**<br>Understanding age-altered stem cell mechanobiology to develop novel mechanobiology-informed advanced therapies for tissue repair |
| **15:50 – 16:00** | **Ulrich Blache (Switzerland)**<br>Secreted matrix as master of the cell-material interface: Challenges and opportunities |
| **16:05 – 16:30** | Invited Speaker Lecture<br>**Florence Ruggiero (France)** TBA |
| **16:35 – 16:45** | Announcement of the winner |
| **16:45-16:50** | Concluding remarks |

# 2021 ASMB e-Symposium series

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

The ASMB e-Symposium series is sponsored by:
Matrix Biology and Matrix Biology Plus, published by Elsevier
https://www.asmb.net/e-symposia

**All webinars begin at 11:00am EDT.**

## Abstract submission for 2021 e-Symposia now OPEN!

Registration link
https://us02web.zoom.us/webinar/register/2016159972736/WN_asIRuVSzRpWcZ2rzXhN0Lw

**June 10, 2021**

**The contribution of stroma progenitor cells to tissue repair and regeneration**
**Co-sponsored by the Canadian Skin Research Group**

Chaired by: Andrew Leask, *University of Saskatchewan*
with Invited Speakers:

Stimulating wound healing in skin using biological dressings engineered from adipose-derived stromal cells (ASCs)
Julie Fradette, *Université Laval/ LOEX*

*C*CN2 expression by collagen-lineage fibroblasts is essential for fibrosis and metastasis
Andrew Leask*, University of Saskatchewan*

Fibroblast heterogeneity underlying tissue regeneration and fibrosis
Jeff Biernaskie, *University of Calgary*

ISHAS International Society for Hyaluronan Sciences

## **The International Society for Hyaluronan Sciences** (ISHAS) will be hosting a **virtual international conference on June 14-15**.

**Program details** can be found at [ishas.org/ha-2021-conference/schedule](ishas.org/ha-2021-conference/schedule)

**Our keynote speaker is Gijsje Koenderink, Delft University of Technology**

We also have a great line-up of presenters in sessions on:

- HA Metabolism and Synthesis
- HA in Signaling and Cell Biology
- HA in Stem Cells, Development and Aging
- HA in Disease (including the role of HA in COVID-19)
- Advances in HA Biotechnology

ISHAS

We will be choosing additional short talks from submitted abstracts and we will have a virtual poster session!
Finally, we will be presenting the 2021 ***Rooster Prize*** to Vincent C. Hascall (Cleveland Clinic, USA), and announcing the recipient of the new ***Endre Balazs and Janet Denlinger Award***.
Plus we will provide prizes for student and post-doc posters/presentations.
Abstracts can be submitted once registration is complete.

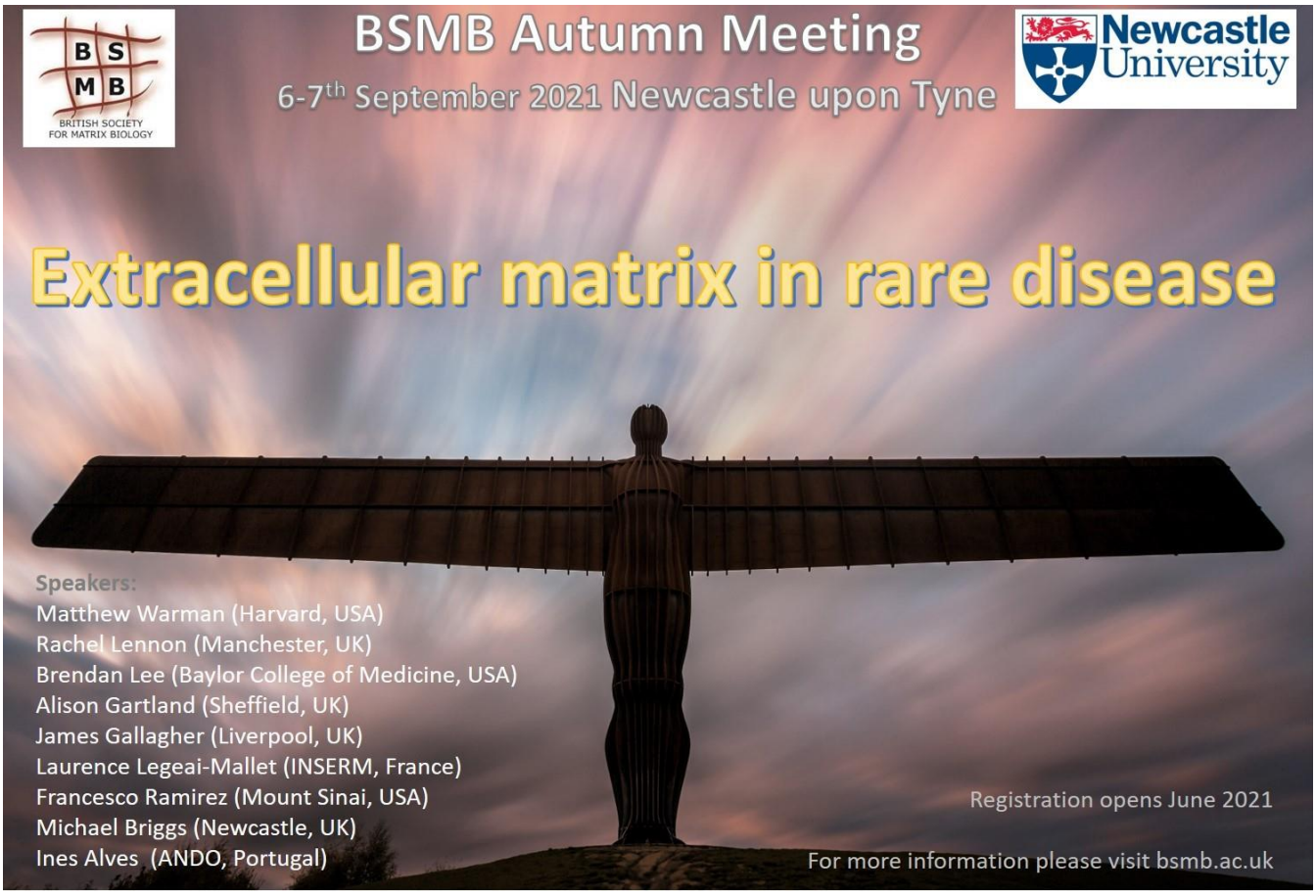
**Registration will close on May 31.**

PLEASE NOTE: Paid-up **Members** and **Trainee Members** of ISHAS can attend the meeting for **FREE!**
If you are a **non-member of ISHAS** and register now for the HA 2021 meeting and then successfully apply for membership of ISHAS, we will carry forward the registration fee towards Membership Dues for 2021.
**Apply for ISHAS Membership here**: [ishas.org/membership-application-form](ishas.org/membership-application-form)
**Please email the meeting co-organizers Larry Sherman (shermanl@ohsu.edu) or Paul Bollyky (pbollyky@stanford.edu) with any questions.**

ISHAS Organizing Committee.

## BSMB Autumn meeting
## 6th-7th September 2021, Newcastle upon Tyne (UK)

Registration opens June 2021
**For more information please visit bsmb.ac.uk**



# Biennal meeting of the American Society for Matrix Biology

## The Matrix In Focus: Matrix, Cells, and Interactions in Health, Disease, Aging, and Regeneration - September 12-15, 2021 - St. Louis, MO (USA)

Registration and abstract submission opened April 15.
https://www.asmb.net/2021-biennial-meeting


The American Society for Matrix Biology is excited to announce that we will hold our postponed 2020 biennial meeting as a hybrid in-person AND virtual meeting from **September 12-15, 2021** in St. Louis, Missouri at the Hyatt Regency St. Louis at the Arch. All recommended COVID-19 protocols will be followed. The meeting program and format of the poster sessions are being adjusted to accommodate the changes required to safeguard the health of all attendees. At the same time, we ensure a dynamic and enjoyable meeting experience that will still include the great science, networking, mentoring, and career development activities typical of ASMB's biennial meetings. For those who are unable to travel to St. Louis, a significant portion of the meeting will be made available virtually in real-time (as well as in recorded format) at a reduced registration rate. Because of time zone differences that could make real-time attendance from remote locations inconvenient, all registrants will have nearly same-day access to recordings of the sessions.

The overall theme of the meeting remains ***"Matrix, Cells, and Interactions in Health, Disease, Aging, and Regeneration."*** The Keynote Speaker will be Dr. Kenneth Yamada of the National Institute of Dental and Craniofacial Research at NIH. In addition to Plenary, Award, and Concurrent Sessions, there will also be trainee-led Special Interest Sessions, Guest Society Symposia, and a new Iozzo Trainee Award competition for students and postdocs who attend either in-person or virtually. Travel Awards targeted to trainees and under-represented minorities will be available.

**Please contact Meeting Chair Jeff Miner** (jeffminer@wustl.edu) **or ASMB Executive Director Kendra LaDuca** (kladuca@asmb.net) **for further information**.

FEBS 2021 ADVANCED COURSE

Matrix Pathobiology, Signaling and Molecular Targets
23 - 28 Sep 2021 | Crete, Greece

The 8th FEBS-ALC course ***"Matrix pathobiology, signaling and molecular targets"*** is designed to cover a wide range of topics, from basic and applied science to clinical applications with a strong focus on recent highlights in the fields of biochemistry, matrix biology, epigenetics, pharmacology and medicine. PhD students and postdoctoral scientists, as well as academic and institute research fellows will have the opportunity to present and discuss their work. Plenary lectures, poster sessions, panel discussions and speaker's corners/meet-the-experts sessions will address and encourage the direct discussions between young scientists and invited experts in a friendly atmosphere.

Organizer: Nikos Karamanos

Dates: September 23rd-28th, 2021

Deadline for applications: June 1st, 2021
Location: Crete (Limenas Hersonissou) – Greece

For any info and updates regarding the course please visit the website:
https://mpst2021.febsevents.org/

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

SHANGHAI CANCER INSTITUTE

SUZHOU MUNICIPAL HOSPITAL

**October 21th-23th, 2021**

**Suzhou, Jiangsu Province, China**

**Sponsor**

Chinese Society of Matrix Biology (CSMB)

**Organizer**

Shanghai Cancer Institute, Suzhou Municipal Hospital

**Topics**

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

**President**

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

**Co-Presidents**

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

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

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

**Abstract Submission**

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

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

Requirements for the applicants of Travel Award:

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

## Save the date!

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

## Proteoglycans GRS & GRC, July 2022, Proctor Academy, Andover, NH, USA

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

## 2023 Collagen Gordon Research Seminar

This conference has been deferred to 2023 due to the ongoing impact of the COVID-19 pandemic.

Colby Sawyer College, NH (USA)

**Chairs: Delfien Syx & Jonathan A. Roth**

https://www.grc.org/collagen-grs-conference/2021/

## 2023 Collagen Gordon Research Conference

This conference has been deferred to July 2023 due to the ongoing impact of the COVID-19 pandemic.

Colby Sawyer College, NH (USA)

**Chair: Taina Pihlajaniemi**

**Vice Chair: Douglas B. Gould**

https://www.grc.org/collagen-conference/2021/

Gordon Research Conferences
*Frontiers of Science*

**Physiological and Disease Relevance and the Underlaying Molecular Properties of Collagens**

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

## 2023 Elastin, Elastic Fibers & Microfibrils Gordon Research Seminar

This conference has been deferred to July 2023 due to the ongoing impact of the COVID-19 pandemic.

Southern New Hampshire University, NH (USA)

**Chairs:** Muthu Lakshmi Muthu & Kirklann N. Lau

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

## 2023 Elastin, Elastic Fibers & Microfibrils Gordon Research Conference

This conference has been deferred to July 2023 due to the ongoing impact of the COVID-19 pandemic.

**Chair:** Dianna Milewicz

**Vice Chair:** Beth A. Kozel

Southern New Hampshire University, NH (USA)

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

Gordon Research Conferences
*Frontiers of Science*

## ISMB membership: become a member of ISMB!

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

## Composition of ISMB council subcommittees

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

**Membership**
Hide Watanabe (Japan)
Suneel Apte (USA)

**Like ISMB on Facebook**
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**Communication group coordinated by** Julia Etich (Germany, Julia.Etich@kgu.de)
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The ISMB correspondents of National Societies for Matrix Biology for Facebook & Twitter

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

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

**The International Society for Matrix Biology (ISMB) Twitter @IntSocMatBio**
Julia Etich, Goethe University Frankfurt (Germany) julia.etich@kgu.de
Valerio Izzi, University of Oulu (Finland) valerio.Izzi@oulu.fi

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

**The Danish Society for Matrix Biology (DSMB) Twitter @DSMB_dk**
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**The Finnish Connective Tissue Society (FSMB)**
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**The French Society for Matrix Biology (SFBMec) Twitter @SFBMEc**
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**The German Society for Matrix Biology (DGMB) Twitter @Matrixbiologie**
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**Matrix Biology Society of Australia and New Zealand (MBSANZ) Twitter @MatrixBioANZ**
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