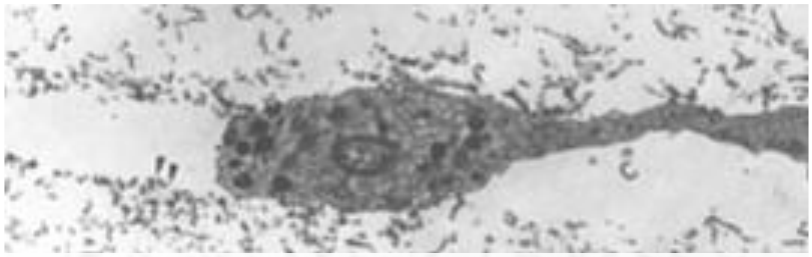

A fibroblast within a tethered lattice, after 13 days, with a cavity surrounding the cell and areas of packed collagen fibrils *(Porter et al. 1998 Wound Rep. Reg. 6: 157-166)*

ISMB NEWSLETTER 33 October 2019
Editor: Sylvie Ricard-Blum

FROM THE PRESIDENT'S DESK

Dear ISMB members,

The major goals of the ISMB are to promote extracellular matrix worldwide, and to support young scientists in the field. The Council discussed in July on the best way to maintain, and if possible to increase, these activities, and decided to make some changes in membership fees and benefits, and to better advertise the activities of the ISMB and national societies. After discussion, the Council decided to increase the membership fee from January 2020 from 50 € to 70 € for regular members but to keep the fees at 20 € for Ph.D. students and researchers in the first 5 years after award of their Ph.D, and to cap travel awards at 700 €. This change should balance the budget of the Society and will allow the award of more travel fellowships to young scientists if possible. It was also decided that, from January 2020, discounted registration to the major matrix biology meetings supported by ISMB (*i.e.* the meeting of the American Society for Matrix Biology, Matrix Biology Europe and Pan-Pacific societies) will continue to apply for Ph.D. students and postdocs who are ISMB members, but not for regular members. The discount will also apply to retired members.

ISMB officers

President	Sylvie Ricard-Blum
Past-President	Liliana Schaefer
Vice-President	Suneel Apte
Secretary	Jo Adams
Treasurer	Ruud Bank
Council Members	
Anthony Day	Julia Etich
Nikos Karamanos	Wei Kong
Megan Lord	Alexandra Naba
Alexander Nyström	Taina Pihlajaniemi
Katia Schenke-Layland	Jean Schwarzbauer
Gerhard Sengle	Hide Watanabe
Anthony Weiss	Chloé Yeung
Ex officio	
Renato Iozzo	Bjorn Olsen

The Council decide to reorganize the Council sub-committees. It was decided that the Meetings and Travel grants Subcommittee and the Membership Subcommittee will be kept as such. The Communication subcommittee has been disbanded and a Communications Group, which is separate from ISMB Council, has been formed. This group includes the 2 early career members of ISMB Council (in 2019, Julia Etich and Chloe Yeung), the correspondents of the national societies listed on page 3 and two new volunteers, Valerio Izzi (Finland) and Pauline Nauroy (Germany). This group is chaired by Julia Etich (Germany), who is responsible for the ISMB Twitter account, and will report to the ISMB Council. We are grateful to her and the Communication Group for their work. Please feel free to contact her (Julia.Etich@kgu.de) and/or other members of the Communication Group if you want to advertise an event and/or a publication in real time.

The ISMB created in 2004 a prize dedicated to the memory of the outstanding matrix biologist, Rupert Timpl, who died on October 20th, 2003. The prize, called the "Rupert Timpl Award", is awarded biannually at the occasion of the Matrix Biology Europe meeting. It is given to young matrix biologists at an early stage of their scientific career, in general below 40 years of age, showing evidence of starting out an independent career in Matrix Biology, and has published the "Best paper in the field of matrix biology" during the two years prior to the year of the Matrix Biology Europe meeting. ISMB has launched the nomination process to identify the 2020 Rupert Timpl Award winner, who will give a plenary lecture during the next Matrix Biology Europe meeting to be held from May, 24th to 28th in Florence (Italy), and will receive a prize of 2,000 €, which is generously sponsored by Elsevier, the publisher of Matrix Biology and Matrix Biology Plus. You are invited as ISMB members to send your nominations for the Awardee to the ISMB Secretary (jo.adams@bristol.ac.uk) by 31st December 2019. The nominations will be voted on by ISMB Council and the winner will be announced in January 2020. In January 2020, ISMB will launch the competition for the next Distinguished Investigator award.

This issue contains the usual items, including reports from the meeting of the Canadian Connective Tissue Society held in Montreal last May and from the Spring Meeting of the British Society in conjunction with Matrix Biology Ireland, held in Liverpool last April. The inaugural lecture of the meeting has been given by Professor Ken Yamada (NIH, USA), who has been awarded the BSMB medal. Anthony Weiss (University of Sydney, Australia) has been given the 2019 Clunies Ross Award by the Australian Academy of Technology and Engineering. We warmly congratulate them for these achievements. In addition, this issue pays tribute to a prominent scientist in our field, Robert Donald Bruce Fraser, who passed away in 2019, thanks to John Ramshaw's contribution, and to Dr. Edward G. 'Ted' Cleary, a former President of the Matrix Biology Society of Australia and New Zealand (M BSANZ), thanks to Megan Lord.

I welcome new members, who joined the ISMB in 2019, and strengthened the ISMB in doing so. I welcome any suggestions you all may have to promote the ISMB and or field, and I am looking forward to seeing you in Florence in May 2020 for the Matrix Biology Europe meeting (http://www.mbe2020.org/) organized by Alberto Passi with the help of the Italian Society for Matrix Biology. The ISMB will provide travel fellowships to both Ph.D. students and postdocs, so please do not forget to apply several months in advance of the meeting, *i.e.* before April 1, 2020 (https://ismb.org/travel-grants-2/). Last, I would like to warmly thank those who contributed to this issue of the newsletter.

Best wishes.

Sylvie Ricard-Blum, President of the International Society for Matrix Biology
sylvie.ricard-blum@univ-lyon1.fr

COMPOSITION OF ISMB COUNCIL SUBCOMMITTEES

Meetings and travel grants
Anthony Day (UK)
Ruud Bank (The Netherlands, chair)
Gerhard Sengle (Germany)

Hide Watanabe (Japan)
Chloé Yeung (Denmark)

Membership
Hide Watanabe (Japan)
Suneel Apte (USA)

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

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

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

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

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The Finnish Connective Tissue Society
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Valerio Izzi, University of Oulu, Finland
Valerio.izzi@oulu.fi

The French Society for Matrix Biology
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Matrix Biology Ireland.
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A.TROTIER1@nuigalway.ie

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

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

Matrix Biology World on Twitter

We are delighted to announce that the ISMB together with National Societies for Matrix Biology continues to strengthen the visibility of Matrix Biology Reasearch on social media. To facilitate the activities of the ISMB and the National Societies for Matrix Biology we are releasing information about upcoming meetings, recent publications, open positions and up-to-date announcements. We are particularly grateful to @ccstorytime, @ValerioIzzi, @PaulineNauroy and @NabaLabUIC for their help to promote our activities on twitter! Are you interested to see your announcements being retweeted and commented? **Please, include @IntSocMatBio to your tweets or contact the representatives of the societies**. We would be happy to share your anouncements with the #MatrixBiology world!

MEETING REPORT

Annual meeting of the Canadian Connective Tissue Society (CCTS), Montreal (Canada), 29-31 May, 2019

The 25th Annual Canadian Connective Tissue Conference took place May 29-31, 2019 at the Shriners Hospital for Children-Canada in Montreal, Quebec, Canada. The aim of the Canadian Connective Tissue Society (CCTS) is to fill the gaps in current scientific and clinical understanding of connective tissues in health and disease through communication of health research evidence between Canadian basic scientists, clinicians, and industrial partners. The annual conference provides the opportunity for scientists, clinicians, students, and other individuals representing the broad scope of connective tissue diseases that affect bones, muscles, skin and joints, to come together and exchange knowledge, to collectively move forward in the field of connective tissue research.

This year's meeting showcased leading scientists and clinicians working in the field of connective tissue in health and disease, including Key Note Speaker Dr. Rene St. Arnaud, Director of Shriners Canada Research Centre, Dr. Kjetil Ask, McMaster University, Dr. Sylvie Ricard-Blum, University of Lyon, Dr. Philippe

Campeau, CHU Sainte-Justine Research, University of Montreal, Dr. Colin Crist, McGill University, Dr. Luda Diatchenko, McGill University, Dr. Julie Fradette, Centre de Recherche en Organogénèse Expérimentale de l'Université Laval/ LOEX, Dr. Ed Harvey, Injury, Repair, and Recovery Program at RI MUHC, Dr. David Holdsworth, Western University, Dr. Saija Kontulainen, University of Saskatchewan, Dr. Roman Krawetz, University of Calgary, and Dr. Lidan You, Department of Industrial and Mechanical Engineering, University of Toronto. In addition, there were 36 talks and 58 posters presented by graduate students and postdoctoral scientists. The hard work during the conference was celebrated at the banquet that also presented "Sing, Dance, Rhyme Your Research" contest and a dance party! This conference was organized by Svetlana Komarova and Derek Rosenzweig from McGill University (Montreal).

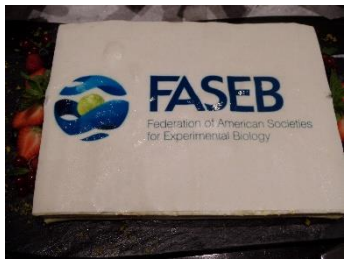
Report on The FASEB Scientific Research Conference "Matricellular Proteins in Inflammation and Tissue Remodeling" (Lisbon, Portugal, July 14 - 19, 2019)

This FASEB SRC was organised for 2019 by Olga Stenina-Adognravi (Lerner Research Institute, Cleveland Clinic) and Joanne Murphy-Ullrich (University of Alabama-Birmingham). The meeting continued an over 20-year history of conferences dedicated to the biology and mechanisms of matricellular proteins. The conference was organized into 9 sessions, each focused on the physiology and/or disease of a specific physiological system, and the functional and mechanistic relationships of selected matricellular proteins to

these processes. In each session, there were 4 – 8 talks, for a total of 40 talks by invited speakers who are recognized leaders in the field, and 13 presentations selected from the submitted abstracts. Two career development events were held during the lunch hours: “Meet the expert”, related to scientific topics of the meeting, and a “Career Development” discussion between early-career and established investigators.

The conference covered all aspects of biology and function of matricellular proteins, and included talks related to thrombospondins, tenascins, SPARC, CCN proteins, periostin and fibulin. A striking feature of this year’s conference was the strong progress of clinical and translation studies as well as basic biological, evolutionary, and molecular investigations. Multiple presentations discussed evidence for potential use of therapeutic strategies aimed at targeting or replicating the activity of particular matricellular proteins in fibrosis, cancer, cardiovascular conditions or pseudoachondroplasia. The keynote speaker presentation by Dr. Didier Stainier, Director of the Max Planck Institute for Heart and Lung Research in Bad Nauheim (Germany) brought a different topic to the meeting. This talk introduced a new emerging aspect of biological regulation: “transcriptional adaptation” that occurs in response to a gene mutation, in which the expression of related gene(s) become upregulated independently of protein feedback loops. Stainier and colleagues have shown that this novel pathway depends on the mutant gene sequence and requires degradation of the mutant mRNA (see Nature 568, 193-197 (2019)). In addition to a better understanding of disease-causing mutations, these findings will greatly help in experimental design of mutant alleles with minimal compensation. The emphasis of the Keynote talk on a newly identified area of molecular cell biology was very much appreciated by conference attendees.

A number of ISMB members were participants at the conference and an “ISMB table” was arranged at dinner one night to facilitate networking by members and those interested in joining ISMB. Discussions related to the Society and the expectations of members. A main point emerging was that early career researchers should be encouraged to join ISMB and retain membership as their careers develop. Options for making ISMB more visible by social media and in local departments were discussed.



The FASEB cake

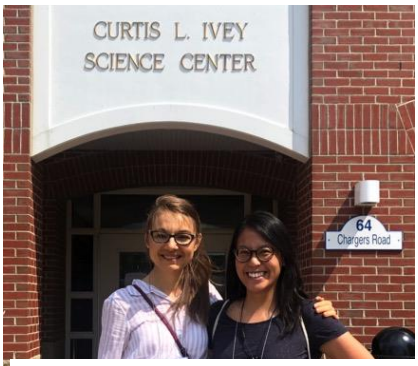
Thanks to financial support from ISMB in the form of a conference award, the conference organizers were able to issue three additional awards to young investigators based on judging of the quality of their poster or oral presentations (judging was carried out by established investigators equipped with standardised scoring sheets). These awards were: Conference Travel Awards to Davy Vanhoutte (Cincinnati Children's Hospital Medical Center, USA) and Georgia Nikoloudaki (Western University - London, CAN) and the Young Investigator Award to Thomas Daubon (INSERM-GBM Team - University Bordeaux - Pessac, FRA). Many thanks to ISMB for making these awards possible.

Jo Adams.

Reports on the Collagen Gordon Research Seminar & Conference, 13-18 July 2019, New London, NH (USA) by ISMB young members

Chloé Yeung, Institute of Sports Medicine Copenhagen, Denmark

I attended the Collagen GRS and GRC in July, 10 years after my first Collagen GRC, which was also my first international meeting. Together with Joanna Jackow from Columbia University, USA I was asked to be a discussion leader of the first session of selected talks at the GRS. We made sure that we were in keeping with the spirit of previous GRS meetings by initiating discussion and encouraging the early career researchers in the audience to ask questions. The GRS is always a great opportunity for those who are a bit shy to get to know each other and get comfortable to ask those 'naïve' but actually really good questions.



Joanna Jackow & Chloé Yeung in front of the lecture hall

As one of the council members of the ISMB attending the meeting, I encouraged GRS attendees to join the society and told them about what great international travel bursary they can apply for! On Sunday evening, it was great to see the arrival of the attendees for the GRC, of which there were many familiar faces! The open and casual atmosphere that started at the GRS continued through the GRC. Highlights of the meeting for me included the Collagen Transport and Trafficking session. I am slightly biased but I really enjoyed the presentations and the discussions of how a collagen molecule is transported from the ER. The discussion led by Karl Kadler between Vivek Malhotra, Sergey Leikin and David Stephens was stimulating. Another highlight for me were the inspiring talks by Leena Bruckner-Tuderman, Kathy Cheah and Clair Baldock who all gave very excellent talks on different topics, which highlighted the diversity of collagen research from molecule to disease to clinical translation.

I really enjoyed the meeting and got a lot of encouraging feedback on my work at the poster session and career advice. I've now returned to the lab with renewed motivation and great ideas (I hope)! I also met many new researchers whom I look forward to seeing again at future ECM meetings. I would encourage anyone working on collagen to attend the next GRC chaired by Taina Pihlajaniemi and Doug Gould in 2020. The collagen GRS/GRC is a fantastic meeting!

Ying Chow, Leibniz-Forschungsinstitut für Molekulare Pharmakologie, Berlin, Germany

It has been an honour and a pleasure to chair the 2019 collagen GRS. Together with my joint chair, Charlotte Gistelinck from the University of Washington, we invited our keynote and mentors, fundraised, networked and publicized the GRS, read through all the applications, selected 10 talks from nearly 40 abstracts... it was an excellent learning experience thanks to the support of the Gordon Conference administration as well as the guidance of Taina Pihlajaniemi and Emmy Gordon, the Vice-Chair and Chair of the collagen GRC. At the GRS, we had 52 attendees, 48% of whom are PhD students and 41% are postdocs, coming from 38 labs in 11 countries. We did have additional applicants who were unable to attend due to lack of funding— so everyone should encourage their trainees/fellow PhD students and postdocs to become a member of ISMB, which provides travel support to early career scientists! Those were the numbers... but it really hit me on Saturday 13 July in Boston, when I realized that we have a whole conference bus just for our GRS. Once we arrived, it started to run like clockwork: everyone checked in, we gave our opening remarks, and the GRS is underway. Keynote lecture, poster sessions, talks, mentorship panel, and of


Taina Pihlajaniemi, Ying Chow, Charlotte Gistelinck, Emmy Gordon

course a social session thrown in the mix. We are gratified to see the inquiring spirit sparked during the GRS continued through the GRC, with many GRS participants emboldened to lead the discussion as new and upcoming members of the collagen research community. We are so grateful to all those who attended, presented, offered advice, supported the GRS, financially or otherwise. We are waiting for the official results from the evaluation - hopefully positive - so that our elected Chairs of Collagen GRS 2021 (Delfin Syx at U Ghent and Jonathan Roth at Rutgers) can carry on the flame!

Bassil Dekky, University of Pennsylvania, USA

Bassil Dekky on a cruise on Lake Sunapee

As a postdoctoral researcher in Dr. S. Volk lab at University of Pennsylvania, US, I had the opportunity to attend the Collagen Gordon Research Seminar and Conference (GRS & GRC), from July 13th-19th at Colby-Sawyer College in New London, NH, United States. The GRS began two days before the conference, which was for PhD students and Post-docs to get to know each other and to discuss sciences, specifically in the field of Collagen while presenting work by oral and poster presentations.

The Collagen GRC group consists of outstanding researchers from all over the world that provided me with the opportunity to make connections as well as enriched and deepen my knowledge on Collagen. These meetings consisted of a variety of sessions that were extremely organized and covered a large range of Collagens and associated-diseases as well as a diversity of expertise, approaches, and techniques that could help me in my future research. In addition, I had the opportunity to give a talk concerning our work on the role of type III Collagen in the breast cancer microenvironment. After my talk, I received great feedback from other scientists as well as opportunities to make new collaborations with our lab. Moreover, the discussion throughout the six days around the poster sessions were insightful and provided a lot of information and new ideas to further my research.

Besides the scientific sessions, there were social activities organized such as a boat trip, hiking, karaoke, and a soccer game where I was the captain of the “Rest of World Team.” It was wonderful to see everybody from PhD students to senior researches come together and enjoy each other’s company. In summary, I highly encourage others to attend the GRC and, more importantly the GRS for students. Personally, it was an excellent seminar to acquire knowledge in Collagen field, which will help me as a researcher.

Julie Di Martino, Icahn School of Medicine at Mount Sinai, USA

Collagen GRC 2019 was my first GRC meeting. I heard a lot about GRC meetings and I have to say that this meeting met my expectations and beyond! I met a nice community of researchers from all over the world all sharing the common passion for collagens! As the result of this week, I now have new friends, potential collaborators, I feel good about my project (I received very good feedback from every people I met) and I joined the ISBM organization! Count me in for the 50 years of the meeting in 2021! I recommend any scientist early career or senior that are interested in extracellular matrix to join and grow the community! We will share good science and hit the dance floor with an awesome karaoke night!

Collagen GRS 2019 attendees

Power Hour at the Collagen GRC 2019

Collagen GRC Football match between the USA and The Rest of The World

Survivors of the hike up Mount Kearsarge

Reports on the 11th International Conference on Proteoglycans, September-October, 3rd, Kanazawa (Japan) by recipients of an ISMB travel award

Marissa Maciej-Hulme, Radboud University Medical Center, Nijmegen (Netherlands)

Highlights of my attendance at the Proteoglycans 2019 meeting: The 11th International Conference on Proteoglycans was held in Kanazawa, Japan between 28th September-3rd October, where I presented a talk and a poster entitled 'Heparan sulfate/heparin derivatives as novel therapeutics for complement-mediated renal disease'. There were many exceptional talks at the conference and I was especially intrigued by recent work presented by Dr. Romain Vivès who is investigating the structure and role of the sulfatase enzymes. Other fantastic talks were given by Prof. Anthony Day on TGS6/hyaluronic acid crosslinking and its involvement in the alternative pathway of the complement system, mast cells and Hyaluronidase-4, a chondroitin specific hydrolase that cleaves serglycin chondroitin sulphate chains by Dr. Brooke Farrugia, as well as an exciting new shotgun method for the isomeric separation of heparan sulphate oligomers presented by Dr. Rebecca Miller, which will facilitate the development of mass spectrometry heparan sulfate sequencing approaches in the future. In addition to the talks, there were two insightful poster sessions, with posters covering a huge range of proteoglycan topics: from fundamental research into biosynthesis, cell signalling and structural aspects, through to novel technologies and translational applications of proteoglycans. During the conference I had the chance to meet a huge range of Proteoglycan experts and to enter thoughtful discussions about my work in relation to other studies currently progressing in the field. Interest in my research was high and I received a lot of helpful suggestions of how to extend the work.

Jamie Thompson, Centre for Biomolecular Sciences, University of Nottingham (UK)

I am incredibly grateful to have been awarded some financial support from the ISMB to attend the "11th International Conference on Proteoglycans" in Kanazawa, Japan. This International meeting is held every second year in a different country, in place of the Gordon Research Conference. It is a unique meeting in that researchers present a considerable amount of unpublished data, meaning you are presenting and discussing projects at the forefront of the matrix field. There was a wide range of exceptional talks, spanning the roles of proteoglycans in disease, tissue homeostasis, developmental biology, therapeutics and biomaterials. I attended the "Future Leaders Symposium" which preceded the main conference and is designed for early career researchers. Shuji Mizumoto and Brooke Farrugia did an excellent job at creating a relaxed environment for young scientists to network before the main meeting. All of the talks were excellent, and it was really encouraging that the audience were very engaged in the Q&A sessions and discussions after the talks. There were plenty of opportunities to meet other ECRs, and talking to them helped me develop new ideas for my own research. Brooke gave a great talk about how to pitch your research, and I will definitely be using these new communication skills in the future. It was a great opportunity to make new collaborations, and also friends.

My PhD project has been focused on developing a disease model for Multiple Osteochondroma using biomaterials and human stem cells. My project is very multidisciplinary, so it was beneficial to get feedback from some of the leading researchers in the Proteoglycan field. I presented a talk during the "late-breaking topics" session on the first day, and received many interesting comments which opened up discussions about where to next take my research. As a result, I have been able to plan and carry out follow-on experiments since returning to the UK, and these will help me plan and write a publication on this project. Hideto Watanabe, Shuhei Yamada and the rest of the organising committee did an excellent job at organising a truly inspirational and fantastic conference. They organised a trip into the Japanese mountains and the conference dinner was a Japanese banquet, both activities of which brought together PhDs, post docs and PIs alike to create long-lasting and fruitful scientific friendships. Thank you to all of the attendees at the conference for welcoming me into the Proteoglycan field.

POSITIONS AVAILABLE on ISMB website (http://ismb.org/career/)

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 meetings supported by ISMB. The Society sends out newsletters highlighting recent research advances, descriptions of matrix biology resources, new appointments and awards, together with announcements of relevant meetings.

Every two years, the Society presents the Rupert Timpl Award to a young scientist (<40 years old), who is starting on their independent career, for the best paper related to matrix biology published in the previous two years and gives the Distinguished Investigator Award for lifetime achievement in the field of matrix biology. ISMB sponsors travel grants for young scientists to attend international matrix meetings. If you work in the matrix biology area, consider becoming a member of ISMB to support the international matrix community and give your input on ways to improve interactions and communication. See the website www.ismb.org to join, for recent job postings and newsletters.

WELCOME TO NEW MEMBERS

Graduate student

Jonathan Roth Rutgers University, Piscataway, New Jersey, USA

PhD students

Marlies Colman	Center for Medical Genetics Ghent, Ghent, Belgium
Ben Calverley	University of Manchester, Manchester, UK
Danielle O'Loughlin	Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK
Jamie L. Thompson	Centre for Biomolecular Sciences, Nottingham, UK
Luke Souter	Faculty of Biological Sciences, University of Leeds, Leeds, UK
Manula S. Rathnayake	Dept. Biomedical Engineering, University of Melbourne, Victoria, Australia
Tibbe Dhooge	Center for Medical Genetics Ghent, Ghent, Belgium

Postdocs

Aastha Kapoor	Thomas Jefferson University, Philadelphia, PA, USA
Eijiro Akasaka	Department of Dermatology, Medical Center, University of Freiburg, Germany
Jarkko Koivunen	University of Oulu, Oulu, Finland
Johanne Dubail	Institut Imagine, INSERM U1163, Paris, France
Julie Di Martino	Mount Sinai, New York, NY, USA
Luigi Scietti	University of Pavia, Pavia, Italy
Marissa Maciej-Hulme	Radboud University Medical Center, Nijmegen, The Netherlands
Nancy Espinoza	Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico
Rui Tang	University of Illinois at Chicago, Chicago, IL, USA
Thomas Crowley	King's College, London, UK

Principal investigators

Jeffrey H. Miner	Washington University School of Medicine, St. Louis, Missouri, USA
Martin Götte	Department of Gynecology and Obstetrics, Münster University Hospital, Germany
Yasutada Imamura	Department of Chemistry and Life Science, Kogakuin University, Japan
Timothy Mead	Cleveland Clinic, Cleveland, Ohio, USA

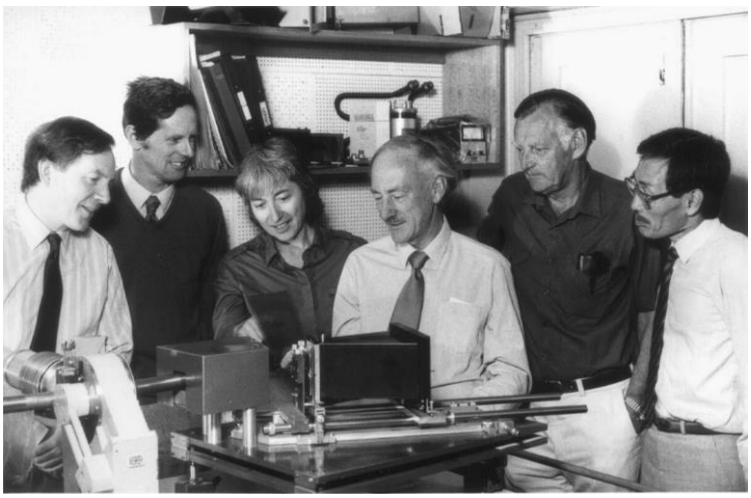
Louise Tzung-Harn Hsieh Department of Microbial Science, University of Surrey, Guildford, UK

OBITUARIES

Bruce Fraser in 1961

Bruce Fraser (1924-2019) pioneered the investigations into the structure of wool keratin, collagen and the silk fibre using X-ray crystallography, electron diffraction and infrared spectroscopy. He began a part-time BSc at Birkbeck college in London University but this was interrupted by World War II. After the war, he completed his BSc (1948) and PhD (1951) degrees at King's College in London. Fraser's PhD work focused on the use of polarised infrared radiation to study the structure of biological materials, and he made important contributions to our ideas about the structure of DNA. In 1951 he was awarded a Nuffield Foundation Fellowship and worked with Maurice Wilkins and Rosalind Franklin on the structure of DNA and with John Randall on the structure of collagen.

In 1952 Bruce Fraser migrated to Australia to take up a position with the recently formed Biochemistry Unit of the Commonwealth Scientific and Industrial Research Organisation (CSIRO). He served the Division of Protein Chemistry at the CSIRO in Melbourne as Assistant Chief for 8 years, as acting Chief from 1983-1985, and as Chief from 1985-1987. Initially he collaborated with George Rogers in a studies of the bilateral structure of the wool fibre but in 1955 became interested in X-ray diffraction, and teamed up with Tom MacRae to apply this technique to the study of fibrous proteins such as wool, hair and collagen. He retired in 1987 to take up a Fogarty Scholarship at the National Institutes of Health (NIH) in Washington undertaking collaborative research with several NIH scientists. After returning to Australia he has continued to publish original contributions to the structure of fibrous protein until the present time. He received many high honours for his work; he was elected Fellow of the Australian Academy of Science in 1978 and was awarded the Research Medal of the Royal Society of Victoria in 1981.
https://www.science.org.au/learning/general-audience/history/interviews-australian-scientists/dr-bruce-fraser-biophysicist. The documents and pictures were kindly provided by John Ramshaw.



Circa 1982: Andrew Miller, David Parry, Barbara Brodsky, Bruce Fraser, Tom MacRae, 'Archie' Suzuki

Dr Edward G. 'Ted' Cleary, **a former President of Matrix Biology Society of Australia and New Zealand (MBSANZ)**, passed away from a heart attack on September 2019. Ted was one of the pioneers in elastic tissue research and wrote some of the most influential early guides on quantifying collagen and elastin, as well as elastin breakdown and associated molecules. He was a Reader at Department of Pathology, University of Adelaide and was a very impressive wine connoisseur. Ted's generous hospitality and extraordinary wine cellar were legendary. He will be sadly missed.
Megan Lord, President of Matrix Biology Society of Australia and New Zealand.

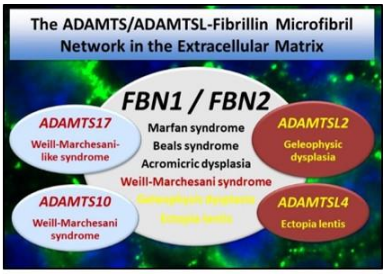
NEWS FROM LABS

Hubmacher Lab (PI: Dirk Hubmacher, Ph.D.)

In 2018, I started my independent laboratory at the Icahn School of Medicine at Mt. Sinai in New York, where it is embedded in the Orthopedic Research Laboratories, which represent the research arm of the Department of Orthopaedics (http://labs.icahn.mssm.edu/hubmacherlab/). The Mt. Sinai hospital is located at the interface of the Upper East Side and East Harlem and attracts with great science and fantastic views of Central Park and the New York skyline. We focus our scientific efforts on defining the physiological and pathological roles of ADAMTS proteases and their substrates as well as on determining the function of ADAMTS-like proteins in the context of rare musculoskeletal disorders. More specifically, we are interested in unraveling the connection between the subset of ADAMTS and ADAMTS-like proteins that are mutated in Weill-Marchesani syndrome and geleophysic dysplasia (*ADAMTS17*, *ADAMTS10*, *ADAMTSL2*), with fibrillin-1 (FBN1) due to the fact that these same disorders can also be caused by specific mutations in the *FBN1* gene. To add to the complexity, mutations in *LTBP2* and *LTBP3* have also been identified in individuals with Weill-Marchesani syndrome or geleophysic dysplasia, respectively, suggesting that a more extensive network of ECM protein may be involved. Our conceptual framework is that fibrillin microfibrils serve as a scaffold for many ECM proteins in many different tissues. To "customize" fibrillin microfibrils, a distinct set of proteins is deployed in each tissue at any given developmental stage that requires this fibrillin microfibril scaffold to exert their tissue specific functions. We primarily take a cell biological and biochemical approach to unravel these ECM networks and we extend our in-vitro findings in animal models for geleophysic dysplasia or Weill-Marchesani syndrome.

The transition into the position as independent group leader was greatly facilitated by the outstanding mentorship that I have received over the years and that I am continuing to receive from Dr. Suneel Apte (Cleveland Clinic Lerner Research Institute) and Dr. Dieter Reinhardt (McGill University), but also from discussions with many other colleagues around the world. Despite some of the usual setbacks, we were able to perform our first experiments in the new lab in the summer of 2018. For now, we are looking forward to the new directions in which our research will lead us and to the continued interactions with the Matrix Biology world. Please feel free to visit us at Mt. Sinai and let's talk "Matrix"!

Sarah, Zerina, Brandon, Nandaraj, Stelios, Dirk



Selected recent publications from the Hubmacher Lab:

Hubmacher D: *Cell-Based Interaction Analysis of ADAMTS Proteases and ADAMTS-Like Proteins with Fibrillin Microfibrils.* Methods Mol. Biol. 2020; 2043:195-206.

Taye N, Karoulias SZ, **Hubmacher D**: *The "other" 15-40%: The Role of Non-Collagenous Extracellular Matrix Proteins and Minor Collagens in Tendon.* J Orthop Res. 2019 (in press).

Hubmacher D, Taye N, Balic Z, Thacker S, Adams SM, Birk DE, Schweitzer R, Apte SS: *Limb- and tendon-specific Adamtsl2 deletion identifies a role for ADAMTSL2 in tendon growth in a mouse model for geleophysic dysplasia.* Matrix Biol. 2019; 82:38-53.

AWARDS

The 2019 Clunies Ross Award

Anthony Weiss, McCaughey Chair in Biochemistry and Professor of Biochemistry and Molecular Biotechnology (University of Sidney, Australia) has been given the 2019 Clunies Ross Award. This is the top award given by the Australian Academy of Technology and Engineering. Further information can be found at https://sydney.edu.au/news-opinion/news/2019/06/13/professor-tony-weiss-wins-prestigious-clunies-ross-award.html

British Society for Matrix Biology Medal Lecture

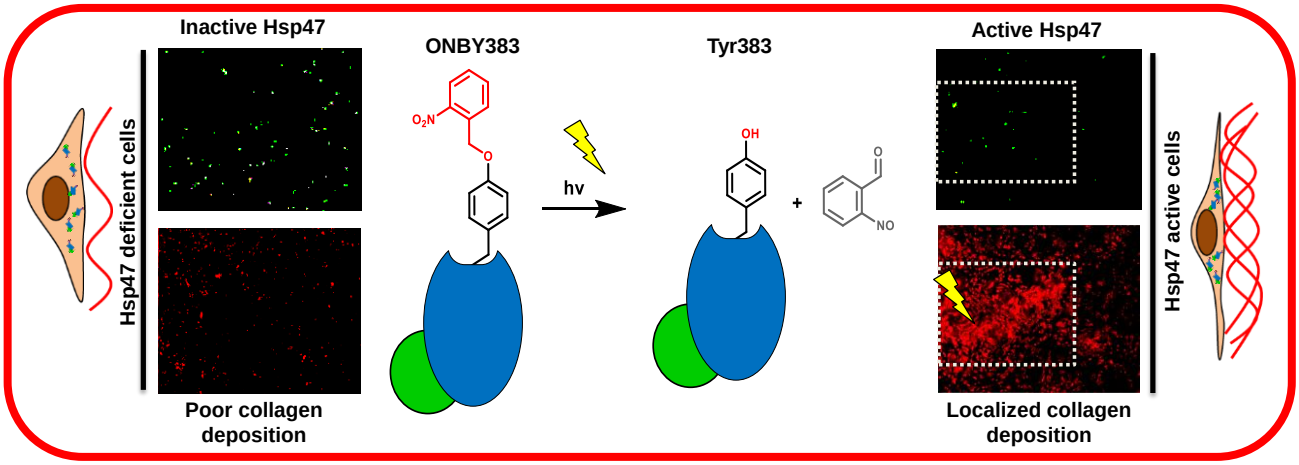
On April the 8th and 9th 2019 the BSMB held its Spring Meeting at the University of Liverpool (UK) in conjunction with Matrix Biology Ireland. The conference, organised by Prof George Bou-Gharios was attended by over 150 delegates from across the world and focused on the them 'Stroma, Niche and Repair'. A highlight of this meeting was the inaugural award of the BSMB medal to **Professor Ken Yamada**.
(MD, PhD, NIH Distinguished Investigator, Chief, Cell Biology Section, NIDCR, NIH, USA), who gave a lecture entitled “Dynamic Cell-Matrix Interactions in 3D Cell Migration and Organ Morphogenesis”

In Focus

Spotlights on methods that other ISMB members may find useful

If you would like to feature in the next newsletter, please email chloe.yeung@gmail.com

Light-responsive HSP47 to enhance collagen biosynthesis and deposition



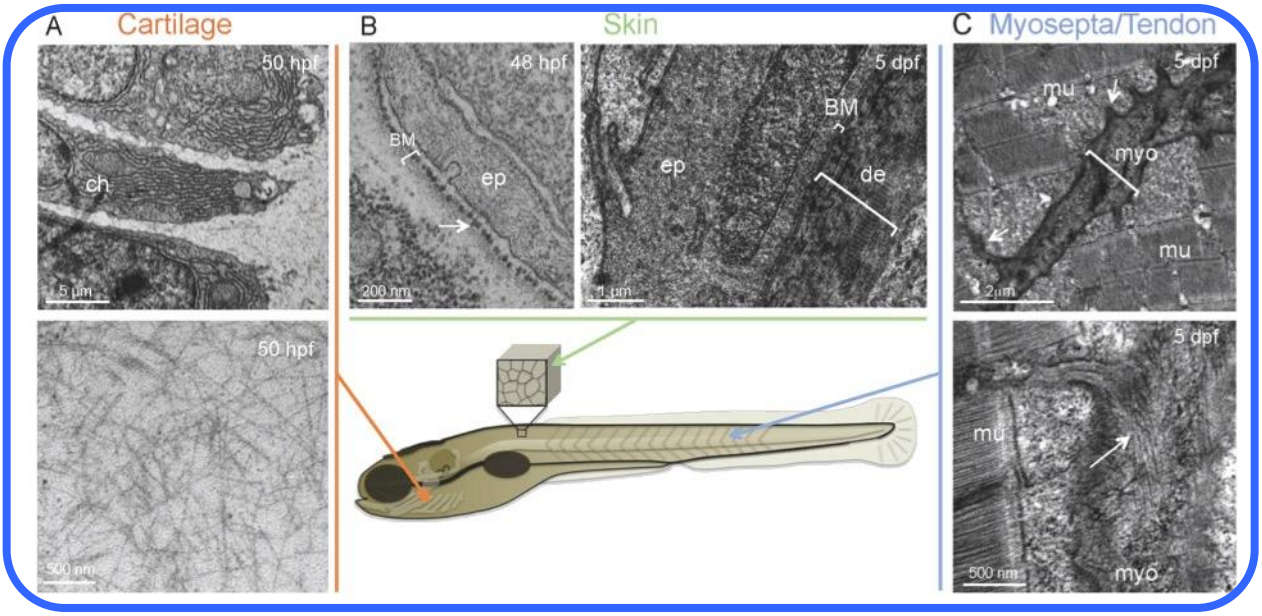
Description: A light-responsive Hsp47 recombinant protein, engineered to control *in situ* the production and assembly of cellular collagen. This novel light-driven tool enables unprecedented fundamental studies of collagen biosynthesis and associated diseases inspiring new therapeutic concepts.
Useful for: Enhancing collagen biosynthesis and deposition for tissue repairs in collagen deficient disorders by light activation, Localizes in ER by simple incubation in the medium without interacting with matrix collagen due to temporary arrest in tissues.
Challenges/Tips: Yields are low; Need to work always in Orange or red light for photo-protection for synthesis and use.
References: https://doi.org/10.1002/advs.201801982
Contact: Essak Khan, PhD student at INM - Leibniz Institute for New Materials gGmbH and Saarland University, **Aránzazu del campo**, Professor at Chemistry Department, Saarland University and Scientific director at INM - Leibniz Institute for New Materials gGmbH
Email: essak.khan@leibniz-inm.de, essakkhan@gmail.com

Zebrafish as a model organism to study the extracellular matrix

Description: Over the last decades, zebrafish (*Danio rerio*) has emerged as a powerful model of human disease [1]. There are many advantages of using this small vertebrate model, including recent advances in genome editing technologies to interrogate gene function. Our lab and many others have already proven that zebrafish is also

instrumental in extracellular matrix research as discussed in our review[2]. The recent characterization of the zebrafish matrisome makes this model even more amenable to the field[3]. Zebrafish is becoming a popular vertebrate model to understand the role of extracellular matrix proteins in development, disease, wound-healing and regeneration[1,4-7]

Useful for: Zebrafish are unmatched compared to other models. Thus, maintenance, raising and feeding are quite simple and the model presents easy and high breeding capacity. Moreover, its small size, its external development and the transparency of embryos and larvae have made of the zebrafish the perfect model to conduct live imaging approaches. This small vertebrate possesses high regeneration capacities that are maintained at adulthood and is therefore a suitable model to investigate the molecular basis of tissue regeneration[7-8]. Lastly, to respect the "3R" principles of ethical experimentations, Zebrafish represents a good alternative model in disease modeling and drug screening[9]. In the 90's, reverse genetic approaches in this small vertebrate has mainly contributed to the zebrafish reputation but the real revolution arose from the CRISPR-Cas9 genome editing technology[10-11]. It offers for the first time the possibility to access to physiological functions not only during the first days of development but also during adulthood and aging. "Omics" data are more and more available and our recent characterization of the zebrafish matrisome[3] shows that ECM proteins are well conserved between mammals and fish; that's partly why we believe that zebrafish will rapidly become one of the leading models in ECM research. In our latest review[2], we specifically discuss evidence highlighting the suitability of the zebrafish model to investigate the diverse functions of collagens in development, tissue regeneration and disease.



Transmission electron microscopy of zebrafish extracellular matrices. Arrows indicate adepidermal granules (B) and finger-like folds (C). Ch, chondrocyte; ep, epidermis; de, dermis; BM, basement membrane; mu, muscle; myo, vertical myosepta; hpf: hour post-fertilisation; dpf, day post-fertilisation. ***From:*** *"Fishing for collagen function: about development, regeneration and disease. Bretaud S, Nauroy P, Malbouyres M, Ruggiero F. Semin Cell Dev Biol. 2019 May; 89:100-108. doi: 10.1016/j.semcdb.2018.10.002."*

Challenges/Tips: The generation of zebrafish stable transgenic lines represented a long and difficult task until recently but is now largely facilitated by the recent advances in genome editing technologies. However, a good knowledge of zebrafish model (raising conditions, zebrafish behavior, ultrastructural organization) is crucial to correctly analyze phenotypes. Specifically, we believe that gene compensation and/or variable expressivity

should be considered in the phenotype analysis of knockout fish, making zebrafish even more reliable as model of human disease.

References:

1. G.J. Lieschke, P.D. Currie, Animal models of human disease: zebrafish swim into view, Nat. Rev. Genet. 8 (2007) 353–367
2. S. Bretaud, P. Nauroy, M. Malbouyres, F. Ruggiero. Fishing for collagen function: About development, regeneration and disease, Semin Cell Dev Biol. 2019 May; 89:100-108.
3. P. Nauroy, S. Hughes, A. Naba, F. Ruggiero, The in-silico zebrafish matrisome: a new tool to study extracellular matrix gene and protein functions, Matrix Biol. 65 (2018) 5–13
4. N.M. Feitosa, R. Richardson, W. Bloch, M. Hammerschmidt, Basement Membrane Diseases in Zebrafish, (2011)
5. R.A. Wyatt, J.Y. Keow, N.D. Harris, C. a Haché, D.H. Li, B.D. Crawford, The zebrafish embryo: a powerful model system for investigating matrix remodeling, Zebrafish 6 (2009) 347–354
6. J.R. Jessen, Recent advances in the study of zebrafish extracellular matrix proteins,Dev. Biol. 401 (2015) 110–121
7. T.M. Tsarouchas, D. Wehner, L. Cavone, T. Munir, M. Keatinge, M. Lambertus, A. Underhill, T. Barrett, E. Kassapis, N. Ogryzko, Y. Feng, T.J. van Ham, T. Becker, C.G. Becker, Dynamic control of proinflammatory cytokines Il-1β and Tnf-α by macrophages in zebrafish spinal cord regeneration.Nat Commun. (2018) Nov 7,9 (1):4670
8. P. Nauroy, A. Guiraud, J.Chlasta,M. Malbouyres, B. Gillet, S. Hughes, E. Lambert, F. Ruggiero, Gene profile of zebrafish fin regeneration offers clues to kinetics, organization and biomechanics of basement membrane. Matrix Biol. (2019) Jan;75-76:82-101.
9. A. Fleming, Zebrafish as an alternative model organism for disease modelling and drug discovery: implications for the 3Rs, NC3Rs 10 (2007) 1–7
10. N. Chang, C. Sun, L. Gao, D. Zhu, X. Xu, X. Zhu, J.W. Xiong, J.J. Xi, Genome editing with RNA-guided Cas9 nuclease in zebrafish embryos, Cell Res. 23 (2013) 465–472
11. W.Y. Hwang, Y. Fu, D. Reyon, M.L. Maeder, S.Q. Tsai, J.D. Sander, R.T. Peterson, J.R.J. Yeh, J.K. Joung, Efficient genome editing in zebrafish using a CRISPR-Cas system, Nat. Biotechnol. 31 (2013) 227–229

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RECENT PAPERS

Pickard, A., Chang, J., Alachkar, N., Calverley, C., Garva, R., Arvan, P., Meng, Q. J., and Kadler, K. E. (2019) Protection of circadian rhythms by the protein folding chaperone, BiP. FASEB J. 33: 7479-7489 Corresponding authors: adam.pickard@manchester.ac.uk and **Karl Kadler** karl.kadler@manchester.ac.uk

Abstract: *Dysregulation of collagen synthesis is associated with disease progression in cancer and fibrosis. Collagen synthesis is coordinated with the circadian clock, which in cancer cells is, curiously, deregulated by endoplasmic reticulum (ER) stress. We hypothesized interplay between circadian rhythm, collagen synthesis, and ER stress in normal cells. Here we show that fibroblasts with ER stress lack circadian rhythms in gene expression upon clock-synchronizing time cues. Overexpression of binding immunoglobulin protein (BiP) or treatment with chemical chaperones strengthens the oscillation amplitude of circadian rhythms. The significance of these findings was explored in tendon, where we showed that BiP expression is ramped preemptively prior to a surge in collagen synthesis at night, thereby preventing protein misfolding and ER stress. In turn, this forestalls activation of the unfolded protein response in order for circadian rhythms to be maintained. Thus, targeting ER stress could be used to modulate circadian rhythm and restore collagen homeostasis in disease.*

Kumra H, Nelea V, Hakami H, Pagliuzza A, Djokic J, Xu J, Yanagisawa H, Reinhardt DP. Fibulin-4 exerts a dual role in LTBP-4L–mediated matrix assembly and function. Proc Natl Acad Sci U S A. 2019 116(41):20428-20437. doi: 10.1073/pnas.1901048116

Corresponding author: dieter.reinhardt@mcgill.ca

Abstract: *Elastogenesis is a hierarchical process by which cells form functional elastic fibers, providing elasticity and the ability to regulate growth factor bioavailability in tissues, including blood vessels, lung, and skin. This process*

requires accessory proteins, including fibulin-4 and -5, and latent TGF binding protein (LTBP)-4. Our data demonstrate mechanisms in elastogenesis, focusing on the interaction and functional interdependence between fibulin-4 and LTBP-4L and its impact on matrix deposition and function. We show that LTBP-4L is not secreted in the expected extended structure based on its domain composition, but instead adopts a compact conformation. Interaction with fibulin-4 surprisingly induced a conformational switch from the compact to an elongated LTBP-4L structure. This conversion was only induced by fibulin-4 multimers associated with increased avidity for LTBP-4L; fibulin-4 monomers were inactive. The fibulin-4–induced conformational change caused functional consequences in LTBP-4L in terms of binding to other elastogenic proteins, including fibronectin and fibrillin-1, and of LTBP-4L assembly. A transient exposure of LTBP-4L with fibulin-4 was sufficient to stably induce conformational and functional changes; a stable complex was not required. These data define fibulin-4 as a molecular extracellular chaperone for LTBP-4L. The altered LTBP-4L conformation also promoted elastogenesis, but only in the presence of fibulin-4, which is required to escort tropoelastin onto the extended LTBP-4L molecule. Altogether, this study provides a dual mechanism for fibulin-4 in 1) inducing a stable conformational and functional change in LTBP-4L, and 2) promoting deposition of tropoelastin onto the elongated LTBP-4L.
https://www.pnas.org/content/early/2019/09/18/1901048116.short?rss=1

Piperigkou Z, Karamanos NK. Dynamic Interplay between miRNAs and the Extracellular Matrix Influences the tumor Microenvironment. Trends Biochem Sci 2019 Jul 6. pii: S0968-0004(19)30140-9. doi: 10.1016/j.tibs.2019.06.007. [Epub ahead of print] Review.
Corresponding authors: zoipip@upatras.gr and N.K.Karamanos@upatras.gr
Abstract: *Expression of miRNAs is critical for the regulation of several cell functions including proliferation, migration, differentiation, and survival, as well as extracellular matrix (ECM) remodeling. The dynamic interplay between miRNAs, ECM macromolecules, and the tumor microenvironment plays critical roles in many aspects of human diseases such as metabolic disorders and cancers. Circulating and secreted miRNAs, via membrane vesicles, affect cell–cell communication and cellularmetabolic pathways, underscoring their significance in tumor progression. The primary goal of this article is to highlight the importance of epigenetic regulatory factors, focusing on miRNA-mediated ECM reorganization and their functional* relationships, and how matrix-mediated miRNAs affect tumor progression.

Bell PA, Solis N, Kizhakkedathu J, Matthew I, Overall CM. Proteomic and N-terminomic TAILS analyses of human alveolar bone proteins: Improved protein extraction methodology and LysargiNase digestion strategies increase proteome coverage and missing protein identification. J Proteome Res. 2019 Oct 11. doi: 10.1021/acs.jproteome.9b00445. [Epub ahead of print]
Corresponding author: chris.overall@ubc.ca
Abstract: *With 2129 proteins still classified by the Human Proteome Organisation Human Proteome Project (HPP) as "missing" without compelling evidence of protein existence (PE) in humans, we hypothesized that in-depth proteomic characterization of tissues that are technically challenging to access and extract would yield evidence for tissue-specific missing proteins. Paradoxically, although the skeleton is the most massive tissue system in humans, as one of the poorest characterized by proteomics, bone falls under the HPP umbrella term as a "rare tissue". Therefore, we aimed to optimize mineralized tissue protein extraction methodology and workflows for proteomic and data analyses of small quantities of healthy young adult human alveolar bone. Osteoid was solubilized by GuHCl extraction, with hydroxyapatite-bound proteins then released by ethylenediaminetetraacetic acid demineralization. A subsequent GuHCl solubilization extraction was followed by solid-phase digestion of the remaining insoluble cross-linked protein using trypsin and then 6 M urea dissolution incorporating LysC digestion. Bone extracts were digested in parallel using trypsin, LysargiNase, AspN, or GluC prior to liquid chromatography-mass spectrometry analysis. Terminal Amine Isotopic Labeling of Substrates was used to purify semitryptic peptides, identifying natural and*

proteolytic-cleaved neo N-termini of bone proteins. Our strategy enabled complete solubilization of the organic bone matrix leading to extensive categorization of bone proteins in different bone matrix extracts, and hence matrix compartments, for the first time. Moreover, this led to the high confidence identification of pannexin-3, a "missing protein", found only in the insoluble collagenous matrix and revealed for the first time by trypsin solid-phase digestion. We also found a singleton proteotypic peptide of another missing protein, meiosis inhibitor protein 1. We also identified 17 proteins classified in neXtprot as PE1 based on evidence other than from MS, termed non-MS PE1 proteins, including ≥9-mer proteotypic peptides of four proteins.

Kiss AA, Somlyai-Popovics N, Kiss M, Boldogkői Z, Csiszár K, Mink M. Novel Phenotypic Elements of Type IV Collagenopathy Revealed by the Drosophila Model. Appl. Sci. 2019, 9, 2083; doi:10.3390/app9102083
Corresponding author: mink@bio.u-szeged.hu
Abstract: *Type IV collagen is proposed to be a key molecule in the evolvement of multicellular animals by forming the architectural unit basement membrane, a specialized form of the extracellular matrix. Functions of the basement membrane include guiding organ regeneration, tissue repair, modulation of cell differentiation, apical–basal polarity identification, cell migration and adhesion, regulation of growth factor signaling gradients, maintenance of tissue architecture and compartmentalization. Type IV collagenopathy is a devastating systemic disease affecting the circulatory, renal and visual systems and the skeletal muscles. It is observed in patients carrying mutations in the COL4A1 gene, which codes for the ubiquitous basement membrane component. Col4a1 mouse mutants display the human symptoms of type IV collagenopathy. We chose the Drosophila melanogaster model as we recorded dominant, temperature-sensitive mutations in the cognate col4a1 gene of the fruit fly and demonstrated phenotypic elements which have not yet been explored in humans or in mouse models. In this paper we show a transition of the Z-discs, normally bordering each sarcomere, to the level of M-discs significantly penetrant in the mutants, uneven distribution of fused mitochondria in the Malpighian tubules of the excretory organ and a loss of sarcomere structure in the visceral muscles in the gut of mutants. Our observations demonstrate the systemic nature of the col4a1 mutations in the fruit fly. However, these traits are elements of the type IV collagen-associated pathology and may provide insights into approaches that can alleviate symptoms of the disease.*

Penk A, Baumann L, Huster D, Samsonov SA. NMR and Molecular Modeling Reveal Specificity of the Interactions between CXCL14 and Glycosaminoglycans. Glycobiology. 2019 29(10):715-725.
Corresponding author: sergey.samsonov@ug.edu.pl
Abstract: *CXCL14, chemokine (C-X-C motif) ligand 14, is a novel highly conserved chemokine with unique features. Despite exhibiting the typical chemokine fold, it has a very short N-terminus of just two amino acid residues responsible for chemokine receptor activation. CXCL14 actively participates in homeostatic immune surveillance of skin and mucosae, is linked to metabolic disorders, fibrotic lung diseases, and possesses strong anti-angiogenic properties in early tumor development. In this work, we investigated the interaction of CXCL14 with various glycosaminoglycans (GAGs) by NMR spectroscopy, microscale thermophoresis, analytical heparin affinity chromatography, and in silico approaches to understand the molecular basis of GAG-binding. We observed different GAG binding modes specific for the GAG type used in the study. In particular, the CXCL14 epitope for heparin suggests a binding pose distinguishable from the ones of the other GAGs investigated (hyaluronic acid, chondroitin sulfate-A/C, -D, dermatan sulfate. This observation is also supported by computational methods that included molecular docking, molecular dynamics and free energy calculations. Based on our results, we suggest that distinct GAG sulfation patterns confer specificity beyond simple electrostatic interactions usually considered to represent the driving forces in protein-GAG interactions. The CXCL14-GAG system represents a promising approach to*

investigate the specificity of GAG protein interactions, which represents an important topic for developing the rational approaches to novel strategies in regenerative medicine.

Samsonov SA, Freza S, Zsilac F. *In silico* analysis of heparin and chondroitin sulfate binding mechanisms of the antiprotozoal drug berenil and pentamidin. Carbohydrate Res3 2019 482: 107742.
Corresponding author: sergey.samsonov@ug.edu.pl
Abstract: *Glycosaminoglycans (GAGs) is a particular class of linear anionic periodic polysaccharides, which play a key role in many cell signaling processes in the extracellular matrix by direct interactions with multiple proteins targets. Because of their periodic nature resulting in experimental challenges to study these molecules, computational approaches recently proved to be successful in complementing the experiments aimed to understand GAG interactions. However, the aspect of GAG binding of small, pharmacologically active molecules is still essentially understudied despite its significance. In this work, we apply computational approaches to rigorously characterize the interactions between GAGs and two trypanosoma active DNA targeting agents, berenil and pentamidine, which mainly differ in the structure of their intramolecular linkers connecting two benzamidine moieties. We thoroughly analyze their binding to heparin and chondroitin 6-sulfate in terms of dynamics, energetics and properties of π-stacked oligomeric structures of the drug molecules formed upon GAG association. Our work contributes to the general understanding of biologically relevant interactions between GAGs and small molecules which has potential impact in drug pharmacology and related therapeutic modalities.*

Bornert O, Nyström A. Cloning and Mutagenesis Strategies for Large Collagens. Methods Mol Biol. 2019;1944:3-15.
Corresponding author: alexander.nystroem@uniklinik-freiburg.de
Abstract: *The size and relatively high GC content of cDNAs are challenges for efficient targeted engineering of large collagens. There are both basic biological and therapeutic interests in the ability to modify collagens, as this would allow for studies precisely describing interactions of collagens with specific interaction partners, addressing consequences of individual disease-causing mutations, and assessing therapeutic applicability of precision medicine approaches. Using collagen VII as an example, we will here describe a strategy for rapid and simple modification of cDNAs encoding large collagens. The method is flexible* and can be used for the creation of point mutations, small or large deletions, and insertion of DNA.

Buchert J, Diederichs S, Kreuser U, Merle C, Richter W. The Role of Extracellular Matrix Expression, ERK1/2 Signaling and Cell Cohesiveness for Cartilage Yield from iPSCs. Int J Mol Sci. 2019 20(17).
Corresponding author: wiltrud.richter@med.uni-heidelberg.de
Abstract: *Current therapies involving chondrocytes or mesenchymal stromal cells (MSCs) remain inefficient in restoring cartilage properties upon injury. The induced pluripotent stem-cell (iPSC)-derived mesenchymal progenitor cells (iMPCs) have been put forward as a promising alternative cell source due to their high proliferation and differentiation potential. However, the observed cell loss during in vitro chondrogenesis is currently a bottleneck in establishing articular chondrocyte generation from iPSCs. In a search for candidate mechanisms underlying the low iPSC-derived cartilage tissue yield, global transcriptomes were compared between iMPCs and MSCs and the cell properties were analyzed via a condensation assay. The iMPCs had a more juvenile mesenchymal gene signature than MSCs with less myofibroblast-like characteristics, including significantly lower ECM- and integrin-ligand-related as well as lower α-smooth-muscle-actin expression. This correlated with less substrate and more cell-cell adhesion, impaired aggregate formation and consequently inferior cohesive tissue properties of the iMPC-pellets. Along lower expression of pro-survival ECM molecules, like decorin, collagen VI, lumican and laminin, the iMPC populations had significantly less active ERK1/2 compared to MSCs. Overall, this study proposes that this ECM and integrin-ligand shortage, together with insufficient pro-survival ERK1/2-activity, explains the loss of a non-*

aggregating iMPC sub-fraction during pellet formation and reduced survival of cells in early pellets. Enhancing ECM production and related signaling in iMPCs may be a promising new means to enrich the instructive microenvironment with pro-survival cues allowing to improve the final cartilage tissue yield from iPSCs.

Cavaco ACM, Eble JA. A 3D Spheroid Model as a More Physiological System for Cancer-Associated Fibroblasts Differentiation and Invasion In Vitro Studies. J Vis Exp. 2019 Aug 8;(150).
Corresponding author: johannes.eble@uni-muenster.de
Abstract: *Defining the ideal model for an in vitro study is essential, mainly if studying physiological processes such as differentiation of cells. In the tumor stroma, host fibroblasts are stimulated by cancer cells to differentiate. Thus, they acquire a phenotype that contributes to the tumor microenvironment and supports tumor progression. By using the spheroid model, we have set up such a 3D in vitro model system, in which we analyzed the role of laminin-332 and its receptor integrin α3β1 in this differentiation process. This spheroid model system not only reproduces the tumor microenvironment conditions in a more accurate way, but also is a very versatile model since it allows different downstream studies, such as immunofluorescent staining of both intra- and extracellular markers, as well as deposited extracellular matrix proteins. Moreover, transcriptional analyses by qPCR, flow cytometry and cellular invasion can be studied with this model. Here, we describe a protocol of a spheroid model to assess the role of CAFs' integrin α3β1 and its ectopically deposited ligand, laminin-332, in differentiation and in supporting the invasion of pancreatic cancer cells.*

Daum R, Brauchle EM, Berrio DAC, Jurkowski TP, Schenke-Layland K. Non-invasive detection of DNA methylation states in carcinoma and pluripotent stem cells using Raman microspectroscopy and imaging. Sci Rep. 2019 9:7014.
Corresponding author: katja.schenke-layland@med.uni-tuebingen.de
Abstract: *DNA methylation plays a critical role in the regulation of gene expression. Global DNA methylation changes occur in carcinogenesis as well as early embryonic development. However, the current methods for studying global DNA methylation levels are invasive and require sample preparation. The present study was designed to investigate the potential of Raman microspectroscopy and Raman imaging as non-invasive, marker-independent and non-destructive tools for the detection of DNA methylation in living cells. To investigate global DNA methylation changes, human colon carcinoma HCT116 cells, which were hypomorphic for DNA methyltransferase 1, therefore showing a lower global DNA methylation (DNMT1$^{-/-}$ cells), were compared to HCT116 wildtype cells. As a model system for early embryogenesis, murine embryonic stem cells were adapted to serum-free 2i medium, leading to a significant decrease in DNA methylation. Subsequently, 2i medium -adapted cells were compared to cells cultured in serum-containing medium. Raman microspectroscopy and imaging revealed significant differences between high- and low-methylated cell types. Higher methylated cells demonstrated higher relative intensities of Raman peaks, which can be assigned to the nucleobases and 5-methylcytosine. Principal component analysis detected distinguishable populations of high- and low-methylated samples. Based on the provided data we conclude that Raman microspectroscopy and imaging are suitable tools for the real-time, marker-independent and artefact-free investigation of the DNA methylation states in living cells.*

Diederichs S, Tonnier V, März M, Dreher SI, Geisbüsch A, Richter W. Regulation of WNT5A and WNT11 during MSC in vitro chondrogenesis: WNT inhibition lowers BMP and hedgehog activity, and reduces hypertrophy. Cell Mol Life Sci. 2019 76(19):3875-3889.
Corresponding author: wiltrud.richter@med.uni-heidelberg.de
Abstract: *Re-directing mesenchymal stromal cell (MSC) chondrogenesis towards a non-hypertrophic articular chondrocyte-(AC)-like phenotype is important for improving articular cartilage neogenesis to enhance clinical cartilage repair strategies. This study is the first to demonstrate that high levels of non-canonical WNT5A followed*

by WNT11 and LEF1 discriminated MSC chondrogenesis from AC re-differentiation. Moreover, β-catenin seemed incompletely silenced in differentiating MSCs, which altogether suggested a role for WNT signaling in hypertrophic MSC differentiation. WNT inhibition with the small molecule IWP-2 supported MSC chondrogenesis according to elevated proteoglycan deposition and reduced the characteristic upregulation of BMP4, BMP7 and their target ID1, as well as IHH and its target GLI1 observed during endochondral differentiation. Along with the pro-hypertrophic transcription factor MEF2C, multiple hypertrophic downstream targets including IBSP and alkaline phosphatase activity were reduced by IWP-2, demonstrating that WNT activity drives BMP and hedgehog upregulation, and MSC hypertrophy. WNT inhibition almost matched the strong anti-hypertrophic capacity of pulsed parathyroid hormone-related protein application, and both outperformed suppression of BMP signaling with dorsomorphin, which also reduced cartilage matrix deposition. Yet, hypertrophic marker expression under IWP-2 remained above AC level, and in vivo mineralization and ectopic bone formation were reduced but not eliminated. Overall, the strong anti-hypertrophic effects of IWP-2 involved inhibition but not silencing of pro-hypertrophic BMP and IHH pathways, and more advanced silencing of WNT activity as well as combined application of IHH or BMP antagonists should next be considered to install articular cartilage neogenesis from human MSCs.

El Bagdadi K, Zaucke F, Meurer A, Straub RH, Jenei-Lanzl Z. Norepinephrine Inhibits Synovial Adipose Stem Cell Chondrogenesis via α2a-Adrenoceptor-Mediated ERK1/2 Activation. Int J Mol Sci. 2019 20(13).
Corresponding author: zsuzsa.jenei-lanzl@friedrichsheim.de
Abstract: In recent years, first evidences emerged that sympathetic neurotransmitters influence *osteoarthritis (OA) manifestation. Joint-resident stem cells might contribute to cartilage repair, however, their chondrogenic function is reduced. The neurotransmitter norepinephrine (NE) was detected in the synovial fluid of trauma and OA patients. Therefore, the aim of this study was to analyse how NE influences the chondrogenesis of synovial adipose tissue-derived stem cells (sASCs). sASCs were isolated from knee-OA patients synovia. After adrenoceptor (AR) expression analysis, proliferation and chondrogenic differentiation in presence of NE and/or α- and β-AR antagonist were investigated. Cell count, viability, chondrogenic and hypertophic gene expression, sulfated glycosaminoglycan (sGAG) and type II collagen content were determined. Key AR-dependent signaling (ERK1/2, PKA) was analyzed via western blot. sASC expressed α1A-, α1B-, α2A-, α2B-, α2C-, and β2-AR in monolayer and pellet culture. NE did not affect proliferation and viability, but 10^{-7} and 10^{-6} M NE significantly reduced sGAG and type II collagen content as well as ERK1/2 phosphorylation. These effects were fully reversed by yohimbine (α2-AR antagonist). Our study confirms the important role of NE in sASC chondrogenic function and provides new insights in OA pathophysiology. Future studies might help to develop novel therapeutic options targeting neuroendocrine pathways for OA treatment.*

Espinoza-Sánchez NA, Götte M. Role of cell surface proteoglycans in cancer immunotherapy. Semin Cancer Biol. 2019 Jul 20. pii: S1044-579X(19)30041-0.
Corresponding author: martingotte@uni-muenster.de
Abstract: *Over the past few decades, understanding how tumor cells evade the immune system and their communication with their tumor microenvironment, has been the subject of intense investigation, with the aim of developing new cancer immunotherapies. The current therapies against cancer such as monoclonal antibodies against checkpoint inhibitors, adoptive T-cell transfer, cytokines, vaccines, and oncolytic viruses have managed to improve the clinical outcome of the patients. However, in some tumor entities, the response is limited and could benefit from the identification of novel therapeutic targets. It is known that tumor-extracellular matrix interplay and matrix remodeling are necessary for anti-tumor and pro-tumoral immune responses. Proteoglycans are dominant components of the extracellular matrix and are a highly heterogeneous group of proteins characterized by the covalent attachment of a specific linear carbohydrate chain of the glycosaminoglycan type. At cell surfaces, these molecules modulate the expression and activity of cytokines, chemokines, growth factors, adhesion*

molecules, and function as signaling co-receptors. By these mechanisms, proteoglycans influence the behavior of cancer cells and their microenvironment during the progression of solid tumors and hematopoietic malignancies. In this review, we discuss why cell surface proteoglycans are attractive pharmacological targets in cancer, and we present current and recent developments in cancer immunology and immunotherapy utilizing proteoglycan-targeted strategies.

Espinoza-Sánchez NA, Győrffy B, Fuentes-Pananá EM, Götte M. Differential impact of classical and non-canonical NF-κB pathway-related gene expression on the survival of breast cancer patients. J Cancer. 2019 10(21):5191-5211.

Corresponding author: martingotte@uni-muenster.de

Abstract: *Inflammation is a well-known driver of carcinogenesis and cancer progression, often attributed to the tumor microenvironment. However, tumor cells themselves are capable of secreting a variety of inflammatory molecules, leading to the activation of specific signaling pathways that promote tumor progression. The NF-κB signaling pathway is one of the most important connections between inflammation and tumorigenesis. NF-κB is a superfamily of transcription factors that plays an important role in several types of hematological and solid tumors, including breast cancer. However, the role of the NF-κB pathway in the survival of breast cancer patients is poorly studied. In this study, we analyzed and related the expression of both canonical and alternative NF-κB pathways and selected target genes with the relapse-free and overall survival of breast cancer patients. We used the public database Kaplan-Meier plotter (KMplot) which includes gene expression data and survival information of 3951 breast cancer patients. We found that the expression of IKKα was associated with poor relapse-free survival in patients with ER-positive tumors. Moreover, the expression of IL-8 and MMP-1 was associated with poor relapse-free and overall survival. In contrast, expression of IKKβ, p50, and p65 from the canonical pathway, and NIK and RELB from the alternative pathway correlated with better relapse-free survival also when the patients were classified* by *their hormonal and nodal status. Our study suggests that the expression of genes of the canonical and alternative NF-κB pathways is ultimately critical for tumor persistence. Understanding the communication between both pathways would help to find better therapeutic and prophylactic targets to prevent breast cancer progression and relapse.*

Etich J, Koch M, Wagener R, Zaucke F, Fabri M, Brachvogel B. Gene Expression Profiling of the Extracellular Matrix Signature in Macrophages of Different Activation Status: Relevance for Skin Wound Healing. Int J Mol Sci. 2019 20(20).

Corresponding author: julia.etich@kgu.de

Abstract: *The extracellular matrix (ECM) provides structural support for tissue architecture and is a major effector of cell behavior during skin repair and inflammation. Macrophages are involved in all stages of skin repair but only limited knowledge exists about macrophage-specific expression and regulation of ECM components. In this study, we used transcriptome profiling and bioinformatic analysis to define the unique expression of ECM-associated genes in cultured macrophages. Characterization of the matrisome revealed that most genes were constitutively expressed and that several genes were uniquely regulated upon interferon gamma (IFNγ) and dexamethasone stimulation. Among those core matrisome and matrisome-associated components transforming growth factor beta (TGFβ)-induced, matrix metalloproteinase 9 (MMP9), elastin microfibril interfacer (EMILIN)-1, netrin-1 and gliomedin were also present within the wound bed at time points that are characterized by profound macrophage infiltration. Hence, macrophages are a source of ECM components in vitro as well as during skin wound healing, and identification of these matrisome components is a first step to understand the role and therapeutic value of ECM components in macrophages and during wound healing.*

Heumüller SE, Talantikite M, Napoli M, Armengaud J, Mörgelin M, Hartmann U, Sengle G, Paulsson M, Moali C, Wagener R. C-terminal proteolysis of the collagen VI α3 chain by BMP-1 and proprotein convertase(s) releases endotrophin in fragments of different sizes. J Biol Chem. 2019 294(37):13769-13780.
Corresponding author: catherine.moali@ibcp.fr and raimund.wagener@uni-koeln.de
Abstract: *The assembly of collagen VI microfibrils is a multistep process in which proteolytic processing within the C-terminal globular region of the collagen VI α3 chain plays a major role. However, the mechanisms involved remain elusive. Moreover, C5, the short and most C-terminal domain of the α3 chain, recently has been proposed to be released as an adipokine that enhances tumor progression, fibrosis, inflammation, and insulin resistance and has been named "endotrophin." Serum endotrophin could be a useful biomarker to monitor the progression of such disorders as chronic obstructive pulmonary disease, systemic sclerosis, and kidney diseases. Here, using biochemical and isotopic MS-based analyses, we found that the extracellular metalloproteinase bone morphogenetic protein 1 (BMP-1) is involved in endotrophin release and determined the exact BMP-1 cleavage site. Moreover, we provide evidence that several endotrophin-containing fragments are present in various tissues and body fluids. Among these, a large C2-C5 fragment, which contained endotrophin, was released by furin-like proprotein convertase cleavage. By using immunofluorescence microscopy and EM, we also demonstrate that these proteolytic maturations occur after secretion of collagen VI tetramers and during microfibril assembly. Differential localization of N- and C-terminal regions of the collagen VI α3 chain revealed that cleavage products are deposited in tissue and cell cultures. The detailed information on the processing of the collagen VI α3 chain reported here provides a basis for unraveling the function of endotrophin (C5) and larger endotrophin-containing fragments and for refining their use as biomarkers of disease progression.*

Hinderer S, Schenke-Layland K. Cardiac fibrosis - A short review of causes and therapeutic strategies. Adv Drug Deliv Rev. 2019 May 31. pii: S0169-409X(19)30061-4.
Corresponding author: katja.schenke-layland@med.uni-tuebingen.de
Abstract: *Fibrotic diseases cause annually more than 800,000 deaths worldwide, whereof the majority accounts for lung and cardiac fibrosis. A pathological remodeling of the extracellular matrix either due to ageing or as a result of an injury or disease leads to fibrotic scars. In the heart, these scars cause several cardiac dysfunctions either by reducing the ejection fraction due to a stiffened myocardial matrix, or by impairing electric conductance, or they can even lead to death. Today it is known that there are several different types of cardiac scars depending on the underlying cause of fibrosis. In this review, we present an overview of what is known about cardiac fibrosis including the role of cardiac cells and extracellular matrix in this disease. We will further summarize current diagnostic tools and highlight pre-clinical or clinical therapeutic strategies to address cardiac fibrosis.*

Martins Lima A, Martins Cavaco AC, Fraga-Silva RA, Eble JA, Stergiopulos N. From Patients to Platelets and Back Again: Pharmacological Approaches to Glycoprotein VI, a Thrilling Antithrombotic Target with Minor Bleeding Risks. Thromb Haemost. 2019 Sep 29. doi: 10.1055/s-0039-1695770.
Corresponding author: augusto.martinslima@epfl.ch
Abstract: *Despite significant advances in the treatment of thrombogenic diseases, antiplatelet therapies are still associated with a high bleeding risk. Consequently, potential benefits of preventing thromboembolic events by pharmacological agents need to be balanced with the potential harm of inducing hemorrhage. Glycoprotein VI (GPVI) is a platelet-specific receptor, which plays a crucial role in thrombus formation. GPVI deficiency has been identified in patients who suffer from significant reduction of collagen-induced thrombus formation, with a slight tendency for mild bleeding. However, an isolated GPVI deficiency can reduce thrombus formation while not resulting in severe bleeding. Together, these observations strongly suggest that physiological hemostasis does not require GPVI, but pharmacological GPVI modulation may provide novel "bleeding-free" antithrombotic therapies. In this review, we discuss recent findings regarding the biological role of GPVI in platelet-related disorders and highlight*

the efforts to develop potential therapeutic strategies based on its structure, signaling pathways, and biological effects.

Ramirez Williams L, Brüggemann K, Hubert M, Achmad N, Kiesel L, Schäfer SD, Greve B, Götte M. γ-Secretase inhibition affects viability, apoptosis, and the stem cell phenotype of endometriotic cells. Acta Obstet Gynecol Scand. 2019 Aug 19 doi: 10.1111/aogs.13707. [Epub ahead of print]
Corresponding author: martingotte@uni-muenster.de
Abstract: *INTRODUCTION: Stem cells mediate cyclic regeneration of the endometrium. The upregulated expression of receptors and modulators of the notch signaling pathway in endometriosis suggests an involvement in the pathogenetic process. Here, we investigated the effects of notch pathway inhibition by a γ-secretase inhibitor (GSI) on stemness-associated properties of the epithelial endometriotic cell line 12Z and of primary endometriotic stroma cells. MATERIAL AND METHODS: 12Z cells and primary endometriotic stroma cells of 7 patients were treated with or without GSI, and analyzed for changes in gene expression by TaqMan low-density arrays, quantitative PCR, and flow cytometry. The functional impact of GSI treatment was studied by MTT assay, cell cycle analysis, colony formation assay, annexin V apoptosis assay, and aldehyde dehydrogenase activity assays. RESULTS: In 12Z cells, GSI treatment reduced aldehyde dehydrogenase activity and colony formation, and induced a shift to the G2/M phase of the cell cycle. Cell viability was decreased and apoptosis was increased in both cell models. GSI further induced transcriptional downregulation of the stemness-associated factors leukemia inhibitory factor receptor (LIFR), sex-determining region Y (SRY)- box 2, interferon-induced transmembrane protein 1, and hes-related family bHLH transcription factor with YRPW motif 1, in 12Z cells and in primary cell cultures. Downregulation of LIFR expression by GSI was confirmed at the protein level by flow cytometry. CONCLUSIONS: Our in vitro data suggest that application of GSI may be a worthwhile approach in the treatment of endometriosis that warrants further investigation.*

Roedig H, Damiescu R, Zeng-Brouwers J, Kutija I, Trebicka J, Wygrecka M, Schaefer L. Danger matrix molecules orchestrate CD14/CD44 signaling in cancer development. Semin Cancer Biol. 2019 Aug 11.
Corresponding author: schaefer@med.uni-frankfurt.de
Abstract: *The tumor matrix together with inflammation and autophagy are crucial regulators of cancer development. Embedded in the tumor stroma are numerous proteoglycans which, in their soluble form, act as danger-associated molecular patterns (DAMPs). By interacting with innate immune receptors, the Toll-like receptors (TLRs), DAMPs autonomously trigger aseptic inflammation and can regulate autophagy. Biglycan, a known danger proteoglycan, can regulate the cross-talk between inflammation and autophagy by evoking a switch between pro-inflammatory CD14 and pro-autophagic CD44 co-receptors for TLRs. Thus, these novel mechanistic insights provide some explanation for the plethora of reports indicating that the same matrix-derived DAMP acts either as a promoter or suppressor of tumor growth. In this review we will summarize and critically discuss the role of the matrix-derived DAMPs biglycan, hyaluronan, and versican in regulating the TLR-, CD14- and CD44-signaling dialogue between inflammation and autophagy with particular emphasis on cancer development.*

Sasaki T, von der Mark K, Lanig H. Molecular dynamics simulations on human fibulin-4 mutants D203A and E126K reveal conformational changes in EGF domains potentially responsible for enhanced protease lability and impaired extracellular matrix assembly. Biochim Biophys Acta Proteins Proteom. 2019 1867(9):748-756.
Corresponding author: klaus.mark@fau.de and harald.lanig@fau.de
Abstract: *Fibulin-4 is a 50 kDa glycoprotein of elastic fibers and plays an important role in development and function of elastic tissues. Fibulin-4 consists of a tandem array of five calcium-binding epidermal growth factor-like modules flanked by N- and C-terminal domains. Mutations in the human fibulin-4 gene EFEMP2 have been identified in patients affected with various arteriopathies including aneurysm, arterial tortuosity, or stenosis, but the molecular*

basis of most genotype-phenotype correlations is unknown. Here we present biochemical and computer modelling approaches designed to gain further insight into changes in structure and function of two fibulin-4 mutations (E126K and D203A), which are potentially involved in Ca^{2+} binding in the EGF2 and EGF4 domain, respectively. Using recombinantly produced fibulin-4 mutant and wild type proteins we show that both mutations introduced additional protease cleavage sites, impaired extracellular assembly into fibers, and affected binding to to fibrillin-1, latent TGF-β-binding proteins, and the lysyl oxidase LOXL2. Molecular dynamics studies indicated that the E126K and D203A mutations do not necessarily result in a direct loss of the complexed Ca^{2+} ion after 500 ns simulation time, but in significantly enhanced fluctuations within the connecting loop between EGF3 and EGF4 domains and other conformational changes. In contrast, intentionally removing Ca^{2+} from EGF4 (D203A ΔCa) predicted dramatic changes in the protein structure. These results may explain the changes in protease cleavage sites, reduced secretion and impaired extracellular assembly of the E126K and D203A fibulin-4 mutants and provide further insight into understanding the molecular basis of the associated clinical phenotypes.

Vitale D, Kumar Katakam S, Greve B, Jang B, Oh ES, Alaniz L, Götte M. Proteoglycans and glycosaminoglycans as regulators of cancer stem cell function and therapeutic resistance. FEBS J. 2019 Aug;286(15):2870-2882.
Corresponding author: laualaniz@yahoo.com.ar and martingotte@uni-muenster.de
Abstract: *In contrast to the bulk of the tumor, a subset of cancer cells called cancer stem cells (CSC; or tumor-initiating cells) is characterized by self-renewal, unlimited proliferative potential, expression of multidrug resistance proteins, active DNA repair capacity, apoptosis resistance, and a considerable developmental plasticity. Due to these properties, CSCs display increased resistance to chemo- and radiotherapy. Recent findings indicate that aberrant functions of proteoglycans (PGs) and glycosaminoglycans (GAGs) contribute substantially to the CSC phenotype and therapeutic resistance. In this review, we summarize how the diverse functions of the glycoproteins and carbohydrates facilitate acquisition and maintenance of the CSC phenotype, and how this knowledge can be exploited to develop novel anticancer therapies. For example, the large transmembrane chondroitin sulfate PG NG2/CSPG4 marks stem cell (SC) populations in brain tumors. Cell surface heparan sulfate PGs of the syndecan and glypican families modulate the stemness-associated Wnt, hedgehog, and notch signaling pathways, whereas the interplay of hyaluronan in the SC niche with CSC CD44 determines the maintenance of stemness and promotes therapeutic resistance. A better understanding of the molecular mechanisms by which PGs and GAGs regulate CSC function will aid the development of targeted therapeutic approaches which could avoid relapse after an otherwise successful conventional therapy. Chimeric antigen receptor T cells, PG-primed dendritic cells, PG-targeted antibody-drug conjugates, and inhibitory peptides and glycans have already shown highly promising results in preclinical models.*

Wessely A, Waltera A, Reichert TE, Stöckl S, Grässel S, Bauer RJ. Induction of ALP and MMP9 activity facilitates invasive behavior in heterogeneous human BMSC and HNSCC 3D spheroids. FASEB J. 2019 Jul 31:fj201900925R.
Corresponding author: richard.bauer@ukr.de
Abstract: *Mesenchymal stem cells (MSCs) are multipotent progenitor cells capable of differentiating into adipocytic, osteogenic, chondrogenic, and myogenic lineages. There is growing evidence that MSCs home into the tumor microenvironment attracted by a variety of signals such as chemokines, growth factors, and cytokines. Tumor-homing stem cells may originate from bone marrow-derived MSCs (BMSCs) or adipose tissue-derived MSCs. Recent scientific data suggest that MSCs in combination with tumor cells can either promote or inhibit tumorigenic behavior. In head and neck squamous cell carcinoma (HNSCC), BMSCs are reported to be enriched with a potential negative role. Here, we evaluated the effect of BMSCs from 4 different donors in combination with 4 HNSCC cell lines in a 3-dimensional multicellular spheroid model. Heterogeneous combinations revealed an up-regulation of gene and protein expression of osteogenic markers runt-related transcription factor 2 (RUNX2) and alkaline phosphatase (ALP) together with a substantial secretion of matrix metalloproteinase 9. Moreover, heterogenous*

BMSC/tumor spheroids showed increased invasion compared with homogenous spheroids in a Boyden chamber invasion assay. Furthermore, inhibition of ALP resulted in a substantially decreased spreading of heterogeneous spheroids on laminin-rich matrix. In summary, our data suggest a prometastatic effect of BMSCs combined with HNSCC.-Wessely, A., Waltera, A., Reichert, T. E., Stöckl, S., Grässel, S., Bauer, R. J. Induction of ALP and MMP9 activity facilitate invasive behavior in heterogeneous human BMSC and HNSCC 3D-spheroids.

Zbinden A, Marzi J, Schlünder K, Probst C, Urbanczyk M, Black S, Brauchle EM, Layland SL, Kraushaar U, Duffy G, Schenke-Layland K, Loskill P. Non-invasive marker-independent high content analysis of a microphysiological human pancreas-on-a-chip model. Matrix Biol. 2019 Jun 22. pii: S0945-053X(19)30149-0.
Corresponding author: katja.schenke-layland@med.uni-tuebingen.de and peter.loskill@uni-tuebingen.de
Abstract: *The increasing prevalence of diabetes, its heterogeneity, and the limited number of treatment options drive the need for physiologically relevant assay platforms with human genetic background that have the potential to improve mechanistic understanding and e\xpedite diabetes-related research and treatment. In this study, we developed an endocrine pancreas-on-a-chip model based on a tailored microfluidic platform, which enables self-guided trapping of single human pseudo-islets. Continuous, low-shear perfusion provides a physiologically relevant microenvironment especially important for modeling and monitoring of the endocrine function as well as sufficient supply with nutrients and oxygen. Human pseudo-islets, generated from the conditionally immortalized EndoC-βH3 cell line, were successfully injected by hydrostatic pressure-driven flow without altered viability. To track insulin secretion kinetics in response to glucose stimulation in a time-resolved manner, dynamic sampling of the supernatant as well as non-invasive real-time monitoring using Raman microspectroscopy was established on-chip. Dynamic sampling indicated a biphasic glucose-stimulated insulin response. Raman microspectroscopy allowed to trace glucose responsiveness in situ and to visualize different molecular structures such as lipids, mitochondria and nuclei. In-depth spectral analyses demonstrated a glucose stimulation-dependent, increased mitochondrial activity, and a switch in lipid composition of insulin secreting vesicles, supporting the high performance of our pancreas-on-a-chip model.*

Sun Z, Velázquez-Quesada I, Murdamoothoo D, Ahowesso C, Yilmaz A, Spenlé C, Averous G, Erne W, Oberndorfer F, Oszwald A, Kain R, Bourdon C, Mangin P, Deligne C, Midwood K, Abou-Faycal C, Lefebvre O, Klein A, van der Heyden M, Chenard MP, Christofori G, Mathelin C, Loustau T, Hussenet T, Orend G.
Tenascin-C increases lung metastasis by impacting blood vessel invasions. Matrix Biol. 2019 Jul 6. pii: S0945-053X(19)30128-3. doi: 10.1016/j.matbio.2019.07.001. [Epub ahead of print]
Corresponding author: gertraud.orend@inserm.fr
Abstract: *Metastasis is a major cause of death in cancer patients. The extracellular matrix molecule tenascin-C is a known promoter of metastasis, however the underlying mechanisms are not well understood. To further analyze the impact of tenascin-C on cancer progression we generated MMTV-NeuNT mice that develop spontaneous mammary tumors, on a tenascin-C knockout background. We also developed a syngeneic orthotopic model in which tumor cells derived from a MMTV-NeuNT tumor. Tumor cells were transfected with control shRNA or with shRNA to knockdown tenascin-C expression and, were grafted into the mammary gland of immune competent, wildtype or tenascin-C knockout mice. We show that stromal-derived tenascin-C increases metastasis by reducing apoptosis and inducing the cellular plasticity of cancer cells located in pulmonary blood vessels invasions (BVI), before extravasation. We characterized BVI as organized structures of tightly packed aggregates of proliferating tumor cells with epithelial characteristics, surrounded by Fsp1+ cells, internally located platelets and, a luminal monolayer of endothelial cells. We found extracellular matrix, in particular, tenascin-C, between the stromal cells and the tumor cell cluster. In mice lacking stromal-derived tenascin-C, the organization of pulmonary BVI was significantly affected,*

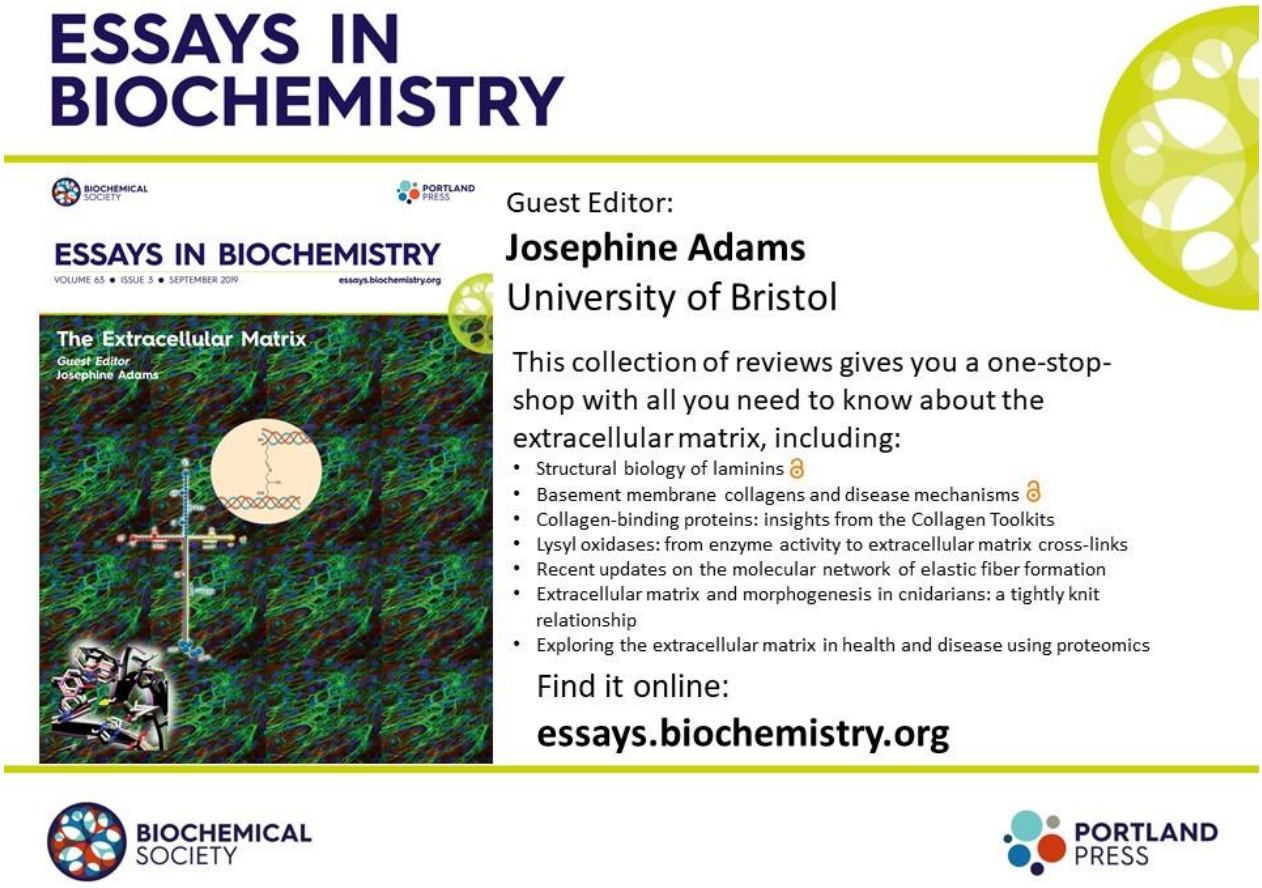
revealing novel functions of host-derived tenascin-C in supporting the integrity of the endothelial cell coat, increasing platelet abundance, tumor cell survival, epithelial plasticity, thereby promoting overall lung metastasis. Many effects of tenascin-C observed in BVI including enhancement of cellular plasticity, survival and migration, could be explained by activation of TGF-β signaling. Finally, in several human cancers, we also observed BVI to be surrounded by an endothelial monolayer and to express tenascin-C. Expression of tenascin-C is specific to BVI and is not observed in lymphatic vascular invasions frequent in breast cancer, which lack an endothelial lining. Given that BVI have prognostic significance for many tumor types, such as shorter cancer patient survival, increased metastasis, vessel occlusion, and organ failure, our data revealing a novel mechanism by which stromal tenascin-C promotes metastasis in human cancer, may have potential for diagnosis and therapy.

SPECIAL ISSUES ON THE EXTRACELLULAR MATRIX

FEBS Journal Special issue Extracellular matrix in health and disease
Pages: 2823-3075 published in August 2019
All articles are open access and could be found at
https://febs.onlinelibrary.wiley.com/toc/17424658/2019/286/15

The extracellular matrix (ECM) is a multifunctional 3D network of interconnected macromolecules that mediate cellular responses in normal and pathological conditions, including wound healing, tissue homeostasis, skeletal and cardiovascular disease, cancer and drug resistance. The potential of targeting ECM components, such as proteoglycans and glycosaminoglycans, matrix-degrading enzymes and miRNAs will serve as a novel tool for innovative diagnostic methods and therapeutic strategies. With this Special Issue on Extracellular Matrix in Health and Disease, The FEBS Journal offers an updated overview of the functional properties and biological roles of several ECM components, highlighting the significance of ECM targeting in disease management**.**

Editor: Nikos Karamanos, University of Patras (Greece)



MATRIX MEETING ANNOUNCEMENTS

6th Matrix Biology Ireland Meeting, November 21-22, 2019, Dublin (Ireland)

Dear All,

On behalf of the organising committee, it is my great pleasure to invite you to the **6th Matrix Biology Ireland Meeting**. The scope of this meeting is to bring together national and international researchers interested in all practical and translational applications of the biology and mechanics of the extracellular matrix in all its forms, including, but not limited to Developmental Biology, Extracellular Matrix Synthesis & Degradation, Glycobiology, Pathophysiology, Degenerative Conditions & Injury, Biomaterials, Tissue Engineering, Regenerative Medicine, Delivery of therapeutics/biologics, 3D in vivo & 3D in vitro Models, ECM Signalling, Tumour Microenvironment, BioEngineering, Advanced Emerging Technologies, ECM Imaging and ECM as Therapeutic.

This year's program aims to stimulate interactive discussions and networking activities, complete with a high level of young investigator talks and presence throughout the program.
Looking forward to seeing you all at the MBI Meeting 2019,
Olga Piskareva

MBI Meeting 2019 Organising Committee:
Dr. Olga Piskareva (RCSI), Chair
Dr. Cian O'Leary (RCSI)
Dr. Caroline Curtin (RCSI)
Dr. Ciara Murphy (RCSI)
Dr. Ronaldo J.F.C. Do Amaral (RCSI)

http://www.mbi.ie/meeting-2019/meeting-home-2019

The Finnish Connective Tissue Society meeting, February, 13, 2020, Helsinki (Finland)

On behalf of The Finnish Connective Tissue Society and The Finnish Society for Cell Biology we would like to invite you to join us in Helsinki for a national scientific meeting. The joint conference of these two societies will be held at the Biomedicum Helsinki (Haartmaninkatu 8, Helsinki, lecture room 3), on February 13th, 2020. The symposium is free of charge and open for both national and international participants. One-day meeting will have keynote presentations and short talks chosen from submitted abstracts. There will be no poster presentations, but students/postdocs are encouraged to submit abstracts for short talks. We welcome abstracts on all aspects of ECM and cell biology. In addition to high quality talks, the meeting schedule will provide plenty of opportunities for informal discussions and networking.

Confirmed speakers: Janine Erler, Sylvie Ricard-Blum, Johanna Ivaska, Sara Wickström, Eija Jokitalo, Sanna Pasonen-Seppänen and Diana Toivola.

Abstracts for short talks may be submitted until 13.12.2019. For detailed information on registration, abstract submission, and program please visit our webpage https://www.sidekudostutkijat.fi/announcements/annual-meeting-2020

The Spring meeting of the British Society for Matrix Biology, April 6th-7th, 2020, University of Surrey, Guildford (UK).

The topic of the symposium will be the pre-clinical and clinical relevance of lipids-matrix interactions. The meeting will be done in collaboration with the British Atherosclerosis Society which will host one session of the event. The meeting promises to be an exciting event with a program enriched by the presence of highly renowned national and international speakers from the private and the academic sectors. Registration will open in January 2020. https://bsmb.ac.uk/meetings/

Matrix Biology Europe meeting, May 24th-28th, Florence (Italy)

Dear Colleagues and Friends,

On behalf of the Organizing Committee, it is a pleasure to welcome you to the MBE 2020 in Florence, Italy. Over the years, the matrix biology community has experienced a terrific development with involvement of several scientific areas ranging from basic science to potential diagnostics, devices, commercial products and therapeutics. The MBE2020 is a perfect opportunity for European scientists to exchange ideas and experiences for further achievements. The program is organized in **9 sessions with a keynote**, **18 international invited speakers** and **45 poster selected for oral presentations**. The program is focusing on research areas at the forefront of the field, from basic aspects of matrix biology research to the most relevant implications in human

health. New technologies and tools are also a critical aspect, providing an overview of state of the art of the area. The selected topics cover key areas, including new roles and perspectives, metabolism and structures, development, bioinformatics, aging and differentiation as well as topics related with human chronic diseases such as cancer, vascular disease, and inflammation. The emerging roles of extracellular matrix molecules in signaling are also addressed in several sessions. Short talks, selected from submitted abstracts based on criteria of novelty and excellence, fit with session topics and aims to promote the research of graduate students, postdocs and new investigators. Poster sessions are also a vital part of the meeting and large part of the program is dedicated to poster sessions.

This international conference is an opportunity to foster active and productive interactions among investigators at all career levels and provide a relaxed environment to promote multi-disciplinary collaborations. The outstanding collaborative attitude of the matrix community is an excellent opportunity for young scientists to network with senior investigators. The target of the conference is an open exchange of ideas between all participants, promoting new research directions to advance development of the field.
Finally, thank you again for joining this exciting scientific meeting. **The conference chair, Alberto Passi.**

Important dates: **Deadline for abstract submission: December, 16th 2019**, **Early deadline registration: February, 14th 2020** (http://www.mbe2020.org/

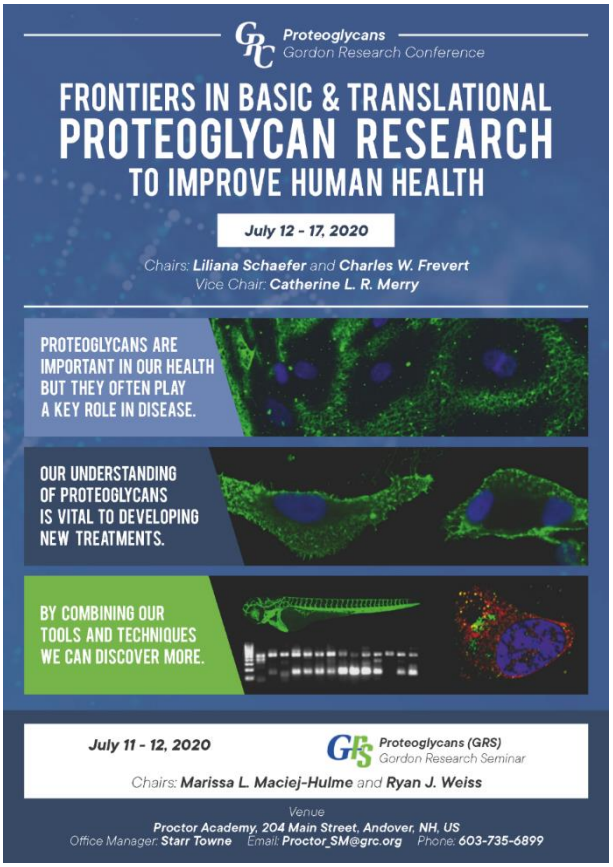
The 4th International Keloid Symposium - Jefferson Matrix Biology and Pathology Symposium June 12-14, 2020, Thomas Jefferson University, Philadelphia (USA)

Proteoglycans GRS and GRC, July 2020, Proctor Academy, Andover, NH (USA)

Proteoglycans Research Seminar, July 11-12, 2020
Chairs: Marissa L. Maciej-Hulme and Ryan J. Weiss

Proteoglycans Research Conference, July 12-17, 2020
Chairs: Liliana Schaefer and Charles W. Frevert
Vice-chair: Catherine L. Merry

https://www.grc.org/proteoglycans-conference/2020/



ASMB 2020 Biennial meeting, November 8-11, 2020, St Louis, MO (USA)

Hyatt Regency at the Arch, St. Louis, MO (USA)
https://www.asmb.net/biennial-meeting