The Matrix Letter

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A Publication of the American Society for Matrix Biology

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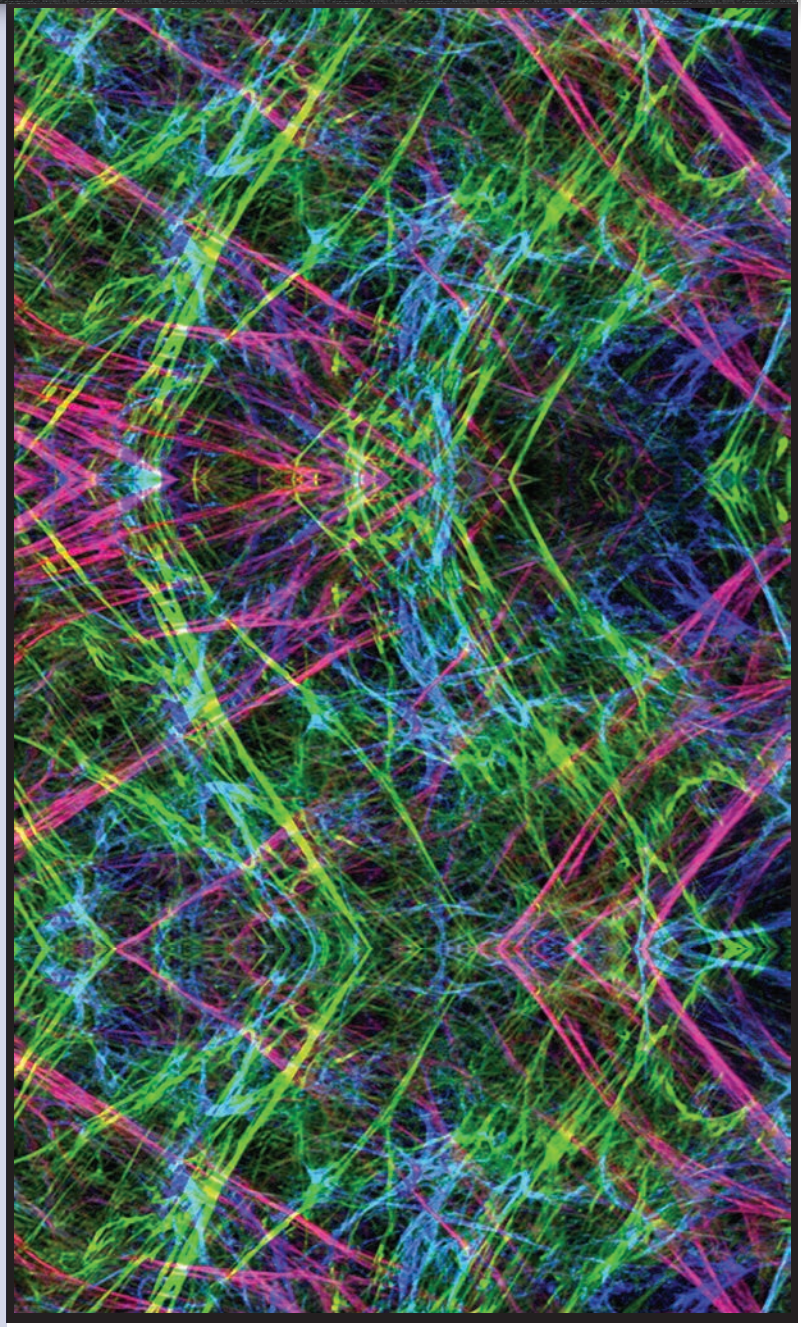


Contents

Calling All Matrix Biologists:

The ASMB promotes the field of matrix biology in order to advance knowledge about the extracellular matrix and to translate this knowledge to improve human health and aging and better treat human disease.

In 2019, we sponsored two ASMB workshops, one on "Fibroblasts: the Arbiters of Extracellular Matrix Remodeling" (organized by Council members Tom Barker and Merry Lindsay) and one on Basement Members (organized by Roy Zent and Jeff Miner). Also, planning for the 2020 Biennial Meeting, led by the Chair (President-elect Jeff Miner) and Program Committee, proceeded in earnest, culminating in selection of the meeting site (St. Louis), dates (Nov. 8-11, 2020) and program topics and speakers.

To further support the matrix biology community, the ASMB promotes the careers of young scientists, women, and under-represented minorities. Meeting and workshop organizers prepare programs that reflect these goals and raise funds to provide travel awards. Special Interest Sessions at the biennial meeting are chances for ASMB postdocs to participate as leaders for topics of interest to them. Look for the call in January to propose an SIS for the 2020 meeting.

The ASMB creates an infrastructure to accomplish our goals. In 2019, the ASMB formed a new partnership with the Histochemical Society, with the American Society for Investigative Pathology, and with our Executive Director Kendra LaDuca. This new partnership, which begins in February 2020, allows ASMB to retain Kendra and promises new opportunities for collaboration with these societies. Our infrastructure also allows us to maintain our important relations with Elsevier and Matrix Biology journals and with other entities interested in supporting ASMB.

Membership has remained around 350 members in the years of the biennial meeting, dropping substantially (to below 200) in the years between the biennial meetings. However, the workshops (begun in 2017 and continued in 2019) have served to maintain interest and membership in the years between biennial meetings. In 2018-2019, membership has remained steady (368 in 2018 and 325 in 2019). Thank you to the workshop organizers!

Membership services and opportunities are also part of ASMB infrastructure. In addition to opportunities to serve on Council and on meeting/workshop organizing committees, members are encouraged to serve on standing committees such as the Communications and Outreach Committee, a new committee which established our ASMB Twitter page and also organized the recent Image Contest (see our ASMB website for the selected images). Thanks to Alexandra Naba and her committee for spearheading these activities.

Check the ASMB website for opportunities to participate! You can also send me an email (shlys@ohsu.edu) if you have questions or wish to volunteer.

Best wishes for the New Year,

Lynn Y. Sakai, Ph.D.

ASMB President

Cover Photo: *Extracellular matrix is the microenvironmental material of a tissue that is produced by local cells. Typically, it is composed of protein polymers enriched with sugary branches (shown here are fibronectin fibers). It is also known for sequestering or storing and then liberating or activating growth, inflammatory and other factors, thus biochemically and/or biophysically affecting local cellular behavior. The confocal generated image shows 6 day chronological matrix deposition by fibroblastic cells. Chronological tagging of cell-derived matrices (or CDMs) was achieved by spiking individually fluorescently tagged fibronectin (as raw materials), and altering fluorophores every other day. (Eti Cuckierman)*

ASMB 2020: Return to St. Louis

In the Fall of 2000, a group of visionary extracellular matrix biologists (see photo) organized the "International Conference on the Biology and Pathology of the Extracellular Matrix" at Washington University School of Medicine in St. Louis so that matrix biologists with diverse interests could share their research findings with peers from around the world. It was there that the ASMB was conceived to ensure the continued health of the matrix biology field and to provide a unified voice for matrix biologists in North America (and beyond). ASMB was incorporated and launched in 2001. As ASMB President-Elect and Chair of the 2020 Biennial Meeting, I am thrilled to be able to bring the meeting back to St. Louis, 20 years after the idea for ASMB was born.

ASMB was conceived 20 years ago. These photos captures early neolithic matrix biologists in their native environment.

The theme of ASMB 2020 is "Matrix, Cells, and Interactions in Health, Disease, Aging, and Regeneration", with a running title of "ASMB 2020: The Matrix in Focus". The meeting will be held Nov. 8-11 (Sunday-Wednesday) at the Hyatt Regency St. Louis at the Arch. The Hyatt is just steps from the tallest man-made monument in the US, the Gateway Arch, which stands 630 feet tall on the west bank of the Mississippi River. The meeting's scientific program will have something for everyone and will begin in earnest on the morning of Sunday, Nov. 8 with Guest Society Symposia, Special Interest Sessions, and Concurrent sessions that will include a talk by an invited speaker followed by talks chosen from submitted poster abstracts. Sunday continues with a welcome address from ASMB President Lynn Sakai and a Plenary session featuring lectures by ASMB award winners, followed by a Welcome reception. To conclude the evening's program, Keynote Speaker Rick Horwitz from the Allen Institute for Cell Biology will deliver his lecture entitled "Creating a State Space of Human Stem Cell Signatures".

Monday and Tuesday mornings will begin with Plenary sessions featuring invited speakers who will focus on important topics chosen by the Program Committee. There will also be a lecture by the International Society for Matrix Biology's Distinguished Investigator Award winner on Tuesday.

Poster sessions with lunch will follow the Plenary sessions, and the afternoon sessions will be a mix of more Concurrent, Guest Society, and Special Interest Sessions with many talks chosen from poster abstracts. Wednesday morning will consist of Iozzo Award lectures by postdocs, the final Plenary session, and the final Concurrent sessions, with adjournment at 1 p.m.

Aside from the main scientific sessions, there will be mentoring breakfasts on Monday and Tuesday mornings. A new aspect of the mentoring program will be a poster "flash talks" session for trainees to present the main points of their posters in 5 minutes with a maximum of 5 slides. The traditional social event on Tuesday evening will be held at City Museum (https://www.citymuseum.org), a very nontraditional venue that defies description and needs to be seen to be believed. Prepare to climb, slide, spin, wander, discover, say "wow!", and of course eat, drink, dance, and maybe even sing. This event will be included in the registration fee and is not to be missed.

ASMB 2020 program, registration, and abstract submission details will be released in early 2020. I hope you will meet me (and your ASMB peers) in St. Louis!

Perhaps looking forward to this issue's cover photo, the photo captures the excitement of the 2000 ECM meeting at Wash U. Eti (page 6) might approve...

Matrix Interactions

ASMB News and Announcements in Brief

Nominations Open for the 2020 ASMB Awards

The nominations committee is now accepting nominations in the following categories. Please send nominations to info@asmb.net by January 31st, 2020.

Founders Award (new): *Young scientists who are in transition toward their first independent career positions whoc demonstrate the highest level of scientific excellence alongside a visible commitment to a career in matrix research and the activities of the ASMB.*

The Junior Investigator Award

A newly established, independent investigator who meets the NIH criteria for a new investigator and who has already made a high-impact finding (or findings). The investigator shall show promise for continued accomplishments.

The Iozzo Award: *To a talented and dedicated matrix biology researcher in the middle of their career. The mid-career investigator should be 5-15 years from their first faculty or equivalent appointment and shall have made significant contributions to our understanding of the matrix.*

The Senior Investigator Award

To be considered for this prestigious award, the nominee must be a current ASMB member, be active in matrix-related research, and be internationally recognized for having made, and continuing to make, important scientific contributions to matrix biology.

Upcoming Events

January 19-23, 2020
Experimental Biology World Congress
2020 London, UK
https://ebworldcongress.org/

April 4-7, 2020
ASBMB Meeting at EB2020:
Thematic Sessions on Glycosylation and Extracellular Matrix in Development, Repair, and Disease
San Diego, CA, USA
https://www.asbmb.org/meeting2020/

April 30-May 2, 2020
11th Symposium on Biologic Scaffolds for Regenerative Medicine
Silverado Resort, Napa, CA, USA
https://www.grc.org/signaling-by-adhesion-receptors-conference/2018/

May 24-28, 2020
Matrix Biology Europe 2020
Convitto della Calza, Florence, IT
http://www.mbe2020.org/

June 9-12, 2020
4th International Keloid Symposium,
Thomas Jefferson University, Philadelphia, PA, USA
http://www.keloidsymposium.com

July 12-17, 2020
Gordon Conference on Proteoglycans
Frontiers in Basic & Translational Proteoglycan Research
Andover, NH, USA
https://www.grc.org/proteoglycans-conference/2020/

November 8-11, 2020
American Society for Matrix Biology 2020
St. Louis, MO, USA
http://www.asmb.net

Election Results

The results of the 2019 election are now in. ASMB congratulates Rolf Brekken (UTSW), Doug Gould (UCSF) and Edna Cuckierman (Fox Chase) on their election to the ASMB council!

The ASMB also recognizes and thanks all candidates who ran and all members who voted. The election process is a cornerstone element of the ASMB.

Thank You to Our Outgoing Councilors

ASMB thanks Tom Barker and Karen Posey, our two outgoing councilors, for their dedicated service on the executive council. Both have served these past three years and have provided important guidance to ASMB. We have been fortunate to have this pair of talented scientists taking a leading role in ASMB.

Summer Workshops 2019

This past summer was the first in which ASMB hosted two workshops, with more than 165 scientists taking part. The longstanding idea of having summer workshops to act as a bridge between the meeting years was implented as part of Suneel Apte's ASMB presidency, and remains both popular and successful. To date, all meetings have been in the Eastern US.

The ASMB/Vanderbilt 2019 Workshop on Basement Membranes was held July 10-12, 2019 at the Vanderbilt University Medical Center in Nashville, TN. Meeting chairs were Roy Zent, Vanderbilt University Medical Center, and Jeffrey Miner Washington University School of Medicine St. Louis. There were eight invited Speakers/Chairs, 28 selected talks from abstracts, and 37 poster presentations. Sixty-three people attended this event and five travel awards were given. University housing was available to participants at an affordable rate - a key feature of the meeting series.

The Session Topics included: Innovative Tools for Basement Membranes Research, Biophysics of Basement Membranes, Basement Membrane Assembly, Diversity of Basement Membranes, Cell-Basement Membrane Interactions, Basement Membranes and Disease, and Therapeutics in Basement Membrane Disease. There was also a Young Investigator Spotlight.

Five Travel Awards were provided. The Awardees were: Pinyuan Tian from the University of Manchester, Allison L. Zajac from the University of Chicago, Meredith J. Giblin from Vanderbilt University, Jill T. Kuwabara from the University of Hawaii at Manoa and Congyue Annie Peng ofClemson University.

The Workshop was supported by Burroughs Wellcome, Elsevier/Matrix Biology and Matrix Biology Plus, and a NIH/NIAMS R13 grant.

In Virginia, the ASMB/University of Virginia 2019 Workshop, "Fibroblasts: The Arbiters of Extracellular Matrix Remodeling" was held from June 23-25, 2019. The meeting was held at the Pinn Conference Hall (School of Medicine) of the University of Virginia in Charlottesville, VA. The meeting Chairs were ASMB Council members Tom Barker of the University of Virginia and Merry Lindsey of the University of Nebraska Medical Center. There were 15 invited speakers and chairs, 21 selected talks from abstracts and 50 posters were presented. Attendees chose from University housing or affordable hotel options within walking distance of the meeting venue. 118 scientists attended this event.

Session Topics included: Fibroblast Origins and Lineages, Fibroblast Heterogeneity and Profiling, Fibroblast ECM Turnover, Dynamics, and Imaging, Fibroblast Signaling Networks, Fibroblasts in the Fibrotic Reticulum, Fibroblast Mechanotransduction, Fibroblasts in Pathology, as well as a Trainee/Young Investigator Career Development Session: How to Thrive in the Fibroblast Research Arena.
There were nine travel awards provided, and they were received by Anne E.C. Nichols, University of Rochester Medical Center, Alexandra M Garvin, University of Arizona College of Medicine Phoenix, Sierra McVeigh, University of Florida, Golnaz Anvari, Temple University, Stephanie D. Burr, The University of Mississippi, Tia M. Jones, Drexel Univeristy, Michele Dill, University of Florida, Linda Berg Luecke, Medical College of Wisconsin; Milwaukee, and Claire Castro, from INSERM.

The Fibroblast workshop was sponsored by UVA Fibrosis Initiative, Elsevier, Bristol Meyer Squibb, and an NIH R13 Grant.

Participants of the Vanderbilt meeting pose for a group photograph.

New Councilors

ASMB congratulates the three new councilors that were recently elected. Each has provided a brief introduction to themselves.

Rolf Brekken received his BA in Biology from Luther College in Decorah, IA and his PhD from UT Southwestern Medical Center. His graduate studies were focused on developing novel therapies that target the vascular compartment of tumors. He was a postdoctoral fellow in Helene Sage's group in the Department of Vascular Biology at the Hope Heart Institute in Seattle, WA where he studied how the extracellular matrix (ECM) contributes to vascular function in tumors. He joined the Department of Surgery at UT Southwestern as faculty in 2002 and was promoted to Associate Professor with tenure in 2009 and Professor in 2015. His laboratory is located in the Hamon Center for Therapeutic Oncology Research. He is currently Chair of the Cancer Biology Graduate Program and Vice Chair of Research in the Department of Surgery and Deputy Director of the Hamon Center at UT Southwestern. Dr. Brekken's laboratory studies the tumor microenvironment. In particular Rolf's group is focused in three areas: 1) pathways that drive epithelial plasticity in tumors; 2) therapeutic immune reactivation; 3) the biology of metastasis. Rolf has been a member of ASMB since 2002 and has attended each ASMB meeting. Rolf notes: *The matrix biology field is interactive and collaborative; ASMB fosters this sense of community to the benefit of all of us interested in ECM biology. I am happy to serve on the ASMB council. Highlighting the exciting opportunities for investigation in the matrix biology and enhancing trainee development are areas of particular interest for me.*

Douglas Gould is a Professor in the Departments of Ophthalmology and Anatomy and the Institute for Human Genetics at the University of California in San Francisco. He is also the Director and Vice Chair of Research for the Department of Ophthalmology.

He earned his Ph. D. at the University of Alberta in Edmonton, Canada where he studied ocular development and the dysgenesis underlying severe forms of congenital glaucoma. For his postdoctoral training, Doug joined the laboratory of Simon John at The Jackson Laboratory and Howard Hughes Medical Institute. Doug's involvement in a forward mutagenesis screen to identify novel genes involved in ocular dysgenesis led to his discovery of the first pathogenic mutations in type IV collagen alpha 1 (COL4A1) in humans and mice. Doug joined UCSF in 2006 and in 2016 was promoted to Professor, appointed as the Director of Research, and named the Denise B. Evans Endowed Chair in Ophthalmology.

The Gould lab has established that COL4A1 and COL4A2 mutations cause a multi-system connective tissues disorder with tissue-specific mechanistic heterogeneity. They continue to use genetic approaches to understand the fundamental biological roles of COL4A1 and COL4A2. The goal of their work is to identify the mechanisms by COL4A1 and COL4A2 mutations cause disease and develop therapeutic interventions.

Doug is the author of nearly 50 peer reviewed research articles and reviews. He is a member of numerous associations and societies including ASMB since 2006, serves on the 2020 ASMB planning committee and is the Vice Chair elect for the 2021 Collagen Gordon Research Conference. He is committed to mentorship and diversity and welcomes the opportunity to serve and give back to the Matrix Biology community.

Edna (Eti) Cukierman is an Associate Professor in Cancer Biology and Co-Director of the Marvin & Concetta Greenberg Pancreatic Cancer Institute at the Fox Chase Cancer Center.

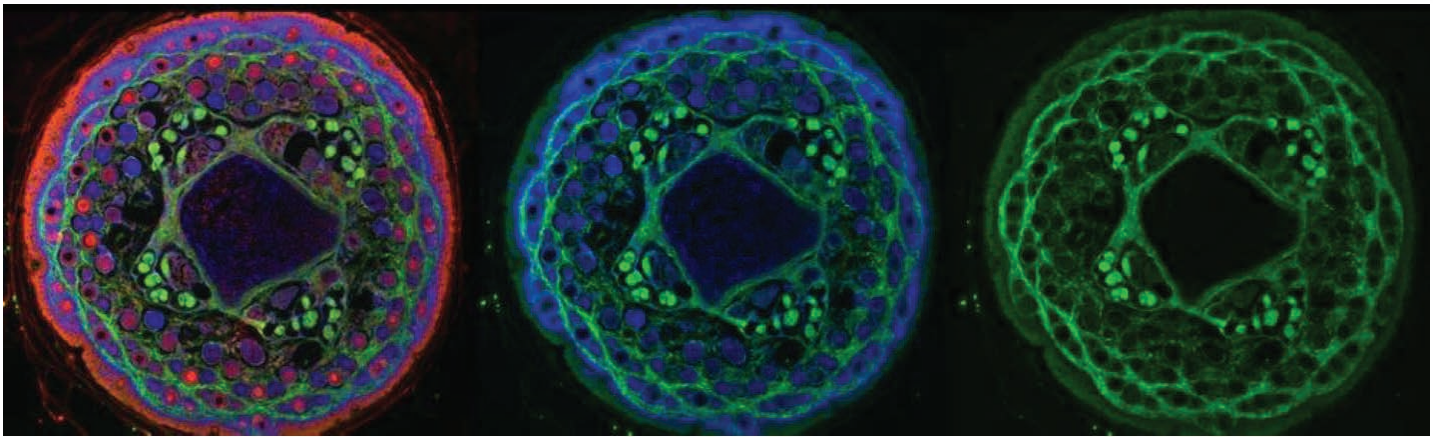
Born and raised in Mexico City, Eti immigrated to Israel in 1986. She attained her doctoral degree, from The Technion Institute of Technology, in 1997. Her doctoral work rendered the biochemical isolation, cloning and characterization of the first ARF-GAP. She then moved, with her spouse and two young children, to Rockville Maryland and conducted her postdoctoral training between the years 1997-2002, under the supervision of Kenneth Yamada, at the National Institute of Dental and Craniofacial Research, National Institutes of Health. It was during this time that she was first exposed to the wonders of extracellular matrix biology. At this time she set out to look for prove of an in vivo fibroblastic cell-matrix adhesion structure (i.e., in vivo focal adhesion). For this, Eti first needed to develop a 3D culturing system that would accurately mimic an in vivo mesenchymal (i.e., fibrous) extracellular matrix. Using an adaptation of the Vlodavsky endothelial culturing system, her system rendered, for the first time, a multi-layered fibroblastic cell-derived extracellular matrix (CDM). Today, CDMs are broadly used, as they allow long term cell culturing while properly mimicking in vivo mesenchymal microenvironments. Eti proceeded to decellularize the CDMs, which together with decellularized extracellular matrices ex vivo, enabled her to unveil the, until then only posited, "3D-matrix adhesion" structure.

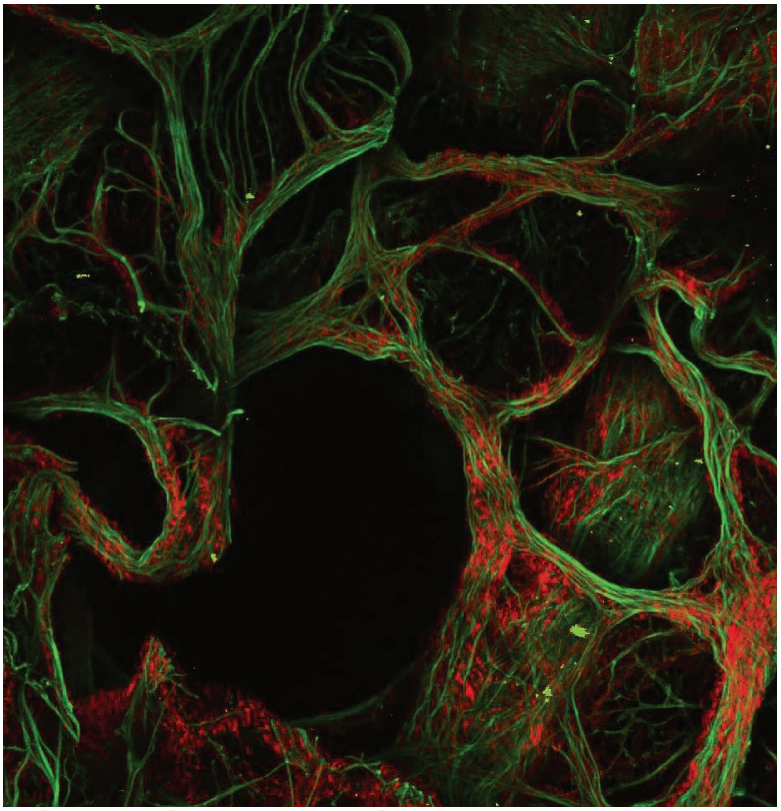
Eti joined Fox Chase Cancer Center in the Fall of 2002, as a tenue track assistant professor in the Cancer Biology program. As a tumor microenvironment devoted scientist, Eti's ongoing research goal is to query the roles that desmoplasia plays in epithelial tumor development and progression. Eti and her team proceeded to establish that cancer-associated fibroblasts (CAFs) produce CDMs that resemble the phenotypes and topographies of cancer-influenced mesenchymal (i.e., desmoplastic) matrices in vivo.

Her group's studies uncovered that cancer-educated CDMs effectively trigger CAF phenotypes and functions upon naïve fibroblastic cells. This now well-established fact, helped her team explain the reason for the observed desmoplastic expansion known as the mesenchymal "field effect." Expansion of desmoplasia, akin to chronic fibrosis, is associated with numerous types of solid epithelial cancers like pancreatic ductal adenocarcinoma. The Cukierman Laboratory uses the modified desmoplastic/fibrous CDM system to determine how CAFs and their matrices regulate functions of cancer and other cells as well as sensitivity (or resistance) to drugs.

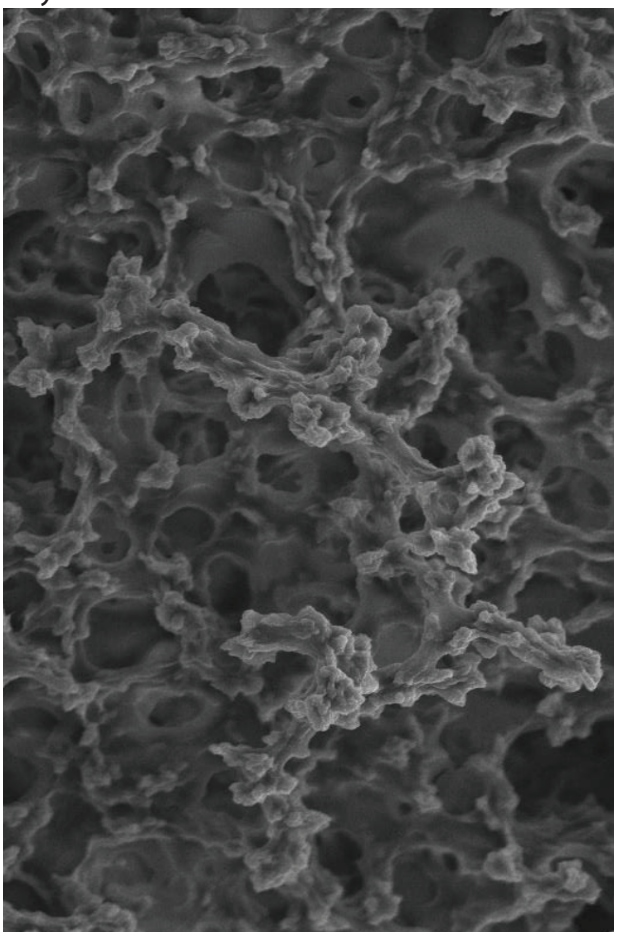
Early on, Eti received a long lasting Career Development Award from the American Association for Cancer Research and, among others, the National Pancreas Foundation Award. Her microscopy work is well known and has been shared with the broad community at public displays. She has presented her work at numerous national and international meetings and has been funded by the NCI continuously since 2004. Eti has served at multiple study sections as an Ad Hoc including at the DOD and NCI (i.e., Tumor Micro Environment Study Section) and as a long standing member of the American Cancer Society (focused on postdoctoral and young investigator awards) and at the NCI's Tumor Progression and Metastasis study sections. She is an active member of various professional organizations (including, AACR, ASCB and ASMB) and serves as Scientific Editor of several journals including Matrix Biology. If elected, Eti would like to broaden ASMB membership and interests to the scientific community. For this, she is eager to share her teaching, mentoring, and professional sponsoring philosophy of "leading by example" and sharing her experience and professional trajectory, as a Latina Woman in STEM, with young trainees and established peers alike.

*The cover of this edition of the **Matrix Letter** features one of Eti's submissions for our social media-driven imaging the ECM contest. The actual submission was the top 40% of the image, which was 'reflected' twice on the version on the cover.*



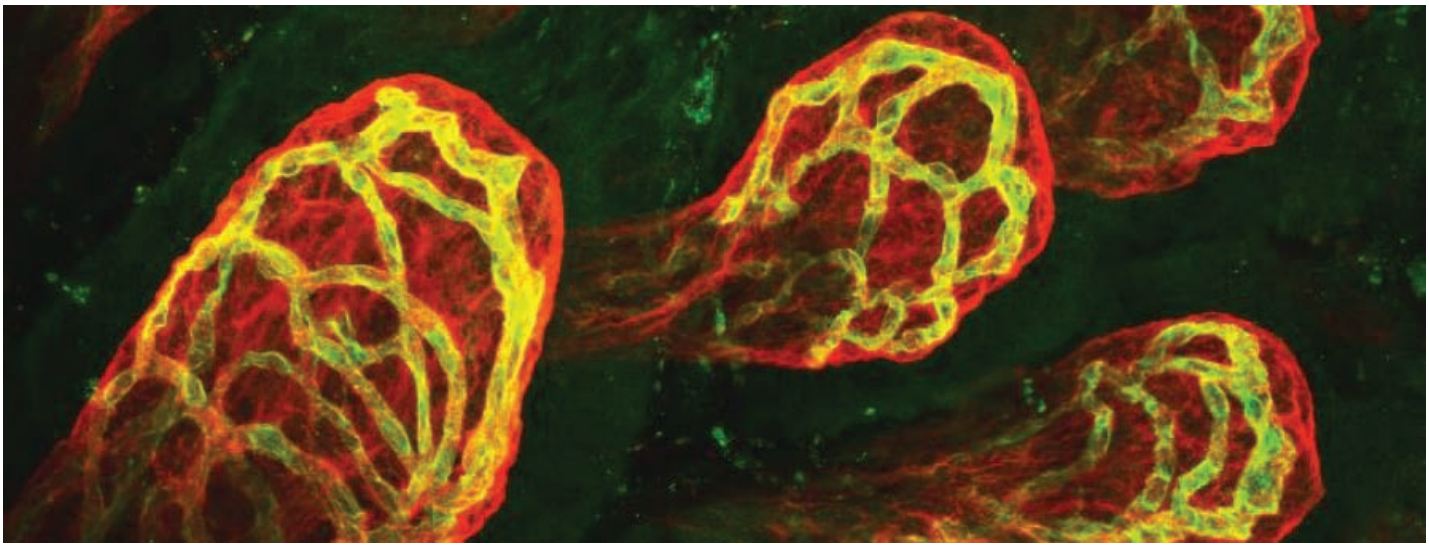


The situation is the same for the composition above "***Stained Glass Collagen***." (*Adam Pickard)*. This image is a whole cross-section of mouse tail showing organisation of type 1 collagen (green), cells are stained with the protein chaperone Bip (red). The mixed grays of the scanning EM image below, ***Bioengineered Hyaluronan-Fibroin Cryogel,*** by William Wagner, show a bioengineered self-associating cryogel of HMW hyaluronan and fibroin as a haunting landscape of caves and canyons.

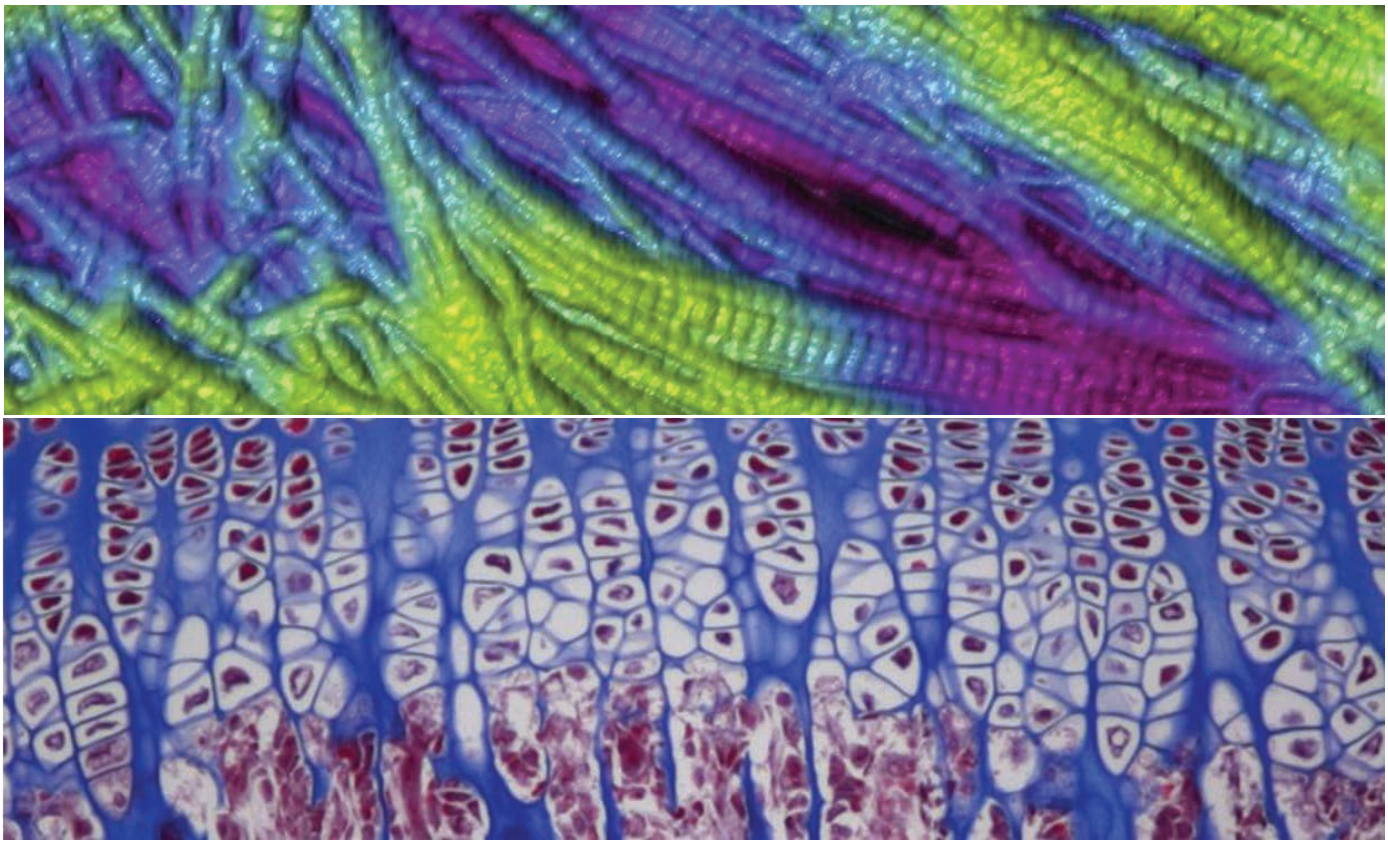


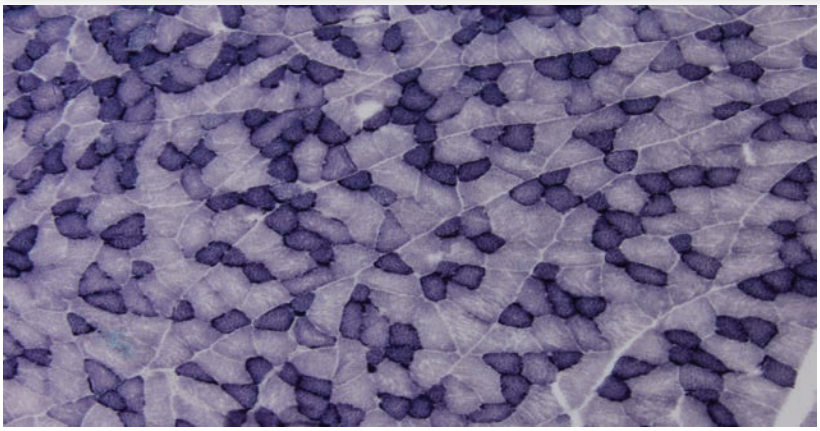
Editorial: Art in the Matrix

The 2019 image contest was truly inspiring for matrix biologists. Now that the contest winners are picked, I have chosen a few images to review for their artistry. Even when we don't know what we are seeing, observers we can objectively appreciate the artistry in these images. This remains true even when we are informed that the underlying tissue is diseased (as in the composition above, ***The Beauty in Disease***) by Ana Karina Perl. This photo is a Second harmonic imaging and 3D reconstruction of Collagen and Elastin in fibrotic lung disease. The beauty of a terrifying disease draws the viewer in. Fascinating and Lovecraftian, the collagen fibrils evoke tentacles. .



The composition above, ***Villi of the Small Intestine***, provides a different but similarly 3-dimensional view of the ECM landscape. In this case *Eva Korpos*' whole mount staining of villi from small intestine shows basement membrane protein (perlecan, red) and blood vessel endothelial cells (green, Meca32) was perfomed. The robust staining reveals the basement membrane that is present around blood vessels, in nerves and beneath the epithelial cell layer of the villi. The patterning of the whole mount contrasts with the SEM on the prior page, but also with the 3D rendering/height map generated by atomic force microscopy in the image below, an area 5 uM in length (*Honor Morris*) that is simply titled ***Collagen fibril organisation within the mouse intervertebral disc as imaged by atomic force microscopy.*** Below this, we switch back to 2 dimensions, with the appropriately titled ***Transition***, - a Trichrome stain by *Bernadette Holdener* showing the trainsition from cartilage to bone. The chondrocytes capture the monastic isolation of a 'cell' perfectly.

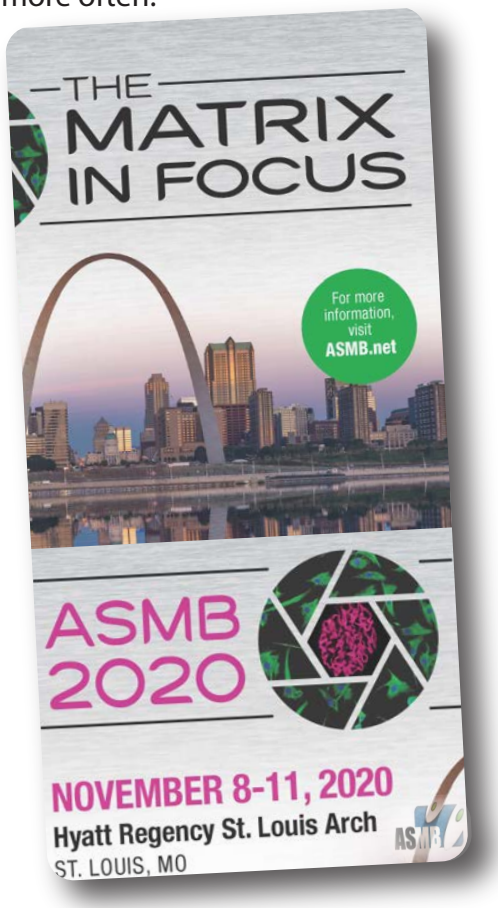




Lastly, we touch on the assymetric geometric composition: ***Muscle Metabolism.*** The detection of succinic dehydrogenase (via alkaline phosphatase) provides complementary lilac hues. I love this image by *Justin Boyer,* and feel like it would make an amazing edition to the wall of any scientist - or non scientist - who appreciates softened art deco or modernism.
/ML

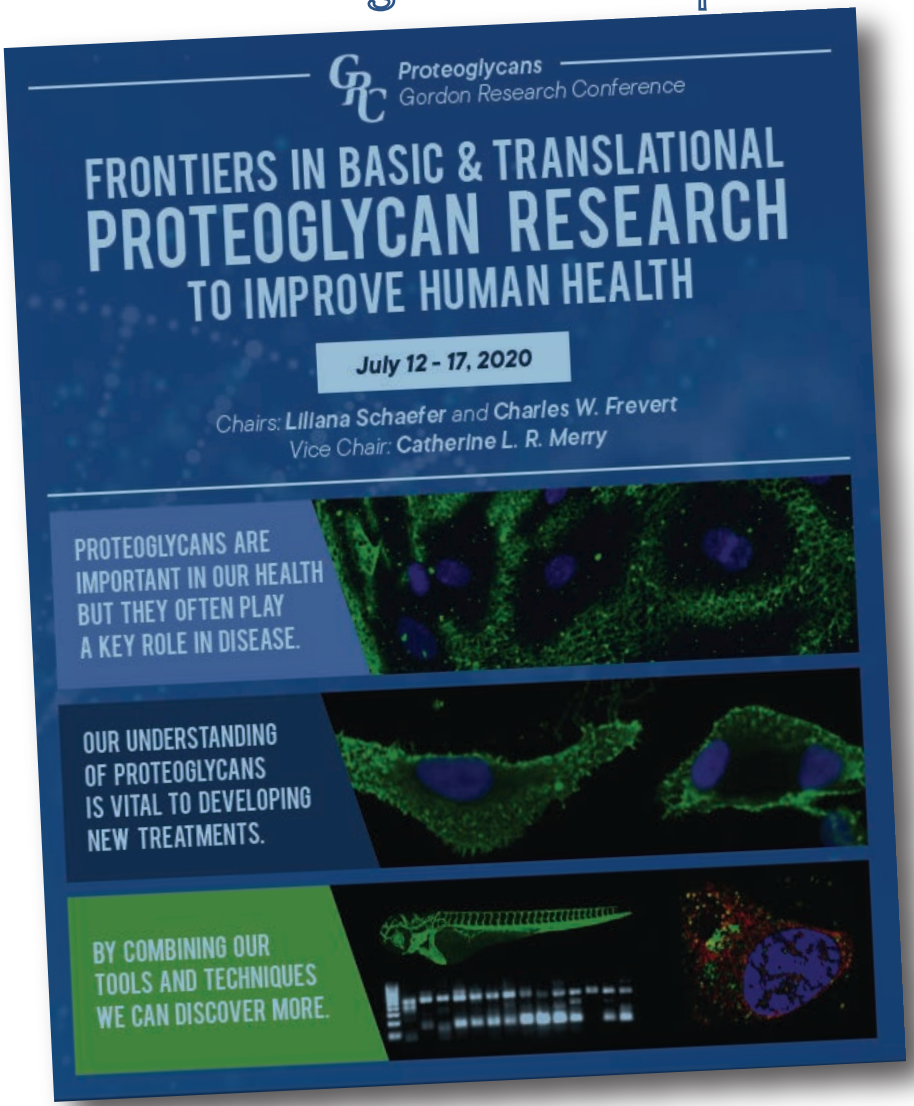
2020 Meetings

The 2020 season of meetings is shaping up beautifully. The central locations for several of the meetings offer the opportunity to see many more of your colleagues, more often.



Call for Special Interest Sessions Proposals

GRC Meeting & Workshop



Call for Special Interest Session Proposals

What are SIS? Special Interest Sessions (SIS) are led by trainees (students or postdocs). SIS should be centered on a fairly focused topic, e.g., "3-D culture systems", "ECM diagnostics" "Fibronectin", "ECM Mineralization". The goals of the SIS are to provide opportunities for investigators working in closely related areas to exchange new data and ideas. The SIS is an outstanding opportunity for junior investigators to present their work, gain experience in organizing a session, and receive feedback from leaders in the field.

What is the Format of a SIS? Each SIS will have a 90 minute block. The format of the SIS is flexible and can be adjusted to fit the ideas and goals of the organizers. Typically, the format of SIS has been similar to other sessions, with 1 (or more) *Discussion Leaders* and 3-4 speakers, but other formats are OK. It is the responsibility of the SIS organizer to recruit speakers and to communicate the program in a timely manner. Fundraising is not necessary, but might be helpful to support travel costs for your speakers.

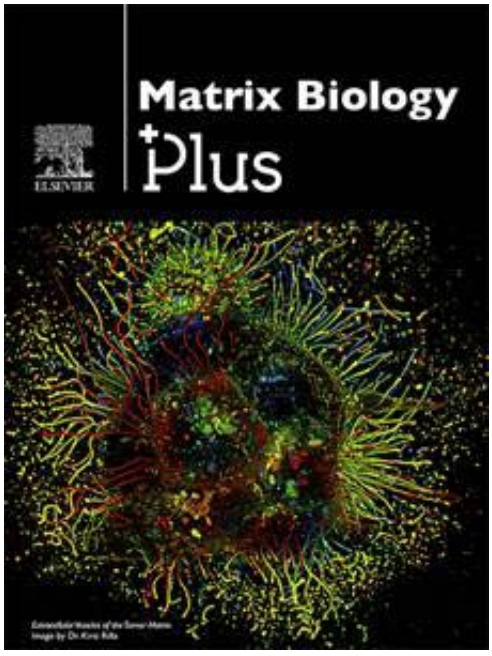
When & Where will the SIS be Held? Space and time has been reserved for 3 SIS during the ASMB meeting. These sessions will be held at the conference hotel (Hyatt Regency St. Louis Arch). Sessions will be incorporated into the main schedule of the meeting for maximum attendance.

The proposal should include a topic title and format and the names and affiliations of the discussion leaders and speakers (if appropriate). We will be happy to discuss your proposals with you.

Send a brief proposal by email to Kendra LaDuca (kladuca@asmb.net) or Jeff Miner (jeffminer@wustl.edu.)

Proposals are due by- February 24, 2020
American Society for Matrix Biology

Publish with
your colleagues.
ASMB-sanctioned journals.



The Matrix Letter

A Publication of the American Society for Matrix Biology

Write for the Matrix Letter!
We feature many types of brief content!
Inquire at Info@ASMB.net

Matrix Mini-reviews

The Matrix Mini-review feature will be a focused summary the contribution of a particular lab in the context of the current state of knowledge in that field. Usually written by young faculty, postdoctoral fellows or even students, the minireview runs about one to two written pages, with a single scientific illustration (and possibly a lab photo), with generally less than 10 references. For PI's, this is a great way to get the word out on your lab's interests when you are recruiting, too.

Matrix Essays

The purpose of a Matrix Essay is to promote or explain a novel hypothesis in the field of Matrix biology. An expressed purpose for such an article would be for garnering supporting (or detracting) evidence and collaborators from the greater ASMB membership. Like the mini-review, the Matrix essay is about one running page and may include a single illustration and up to 10 references.

Letters to the Editor

A letter to the editor should be short and succinct, and will focus on alerting the ASMB membership to recent advances or concerns in our fields and those which will closely impact us. A letter to the editor is limited to 200 words and three references.

Matrix Images

These are submissions of particularly aesthetic and (or) educational images that you are willing to share with the membership, along with a caption explaining the image. These will be openly availabe for distribution, with reference/-credit attributed to your lab.

Matrix Focus

These articles highlight underappreciated or forgotten aspects of matrix biology. They are the perfect place for historical perspectives, and reminders of the different disease linkages that have relevance to our field (*for example, Vitamin C - scurvy - collagen synthesis*).

Reference Format

1) Lewis R, Ravindran S, Wirthlin L, Traeger G, Fernandes RJ, McAlinden A. Disruption of the developmentally-regulated Col2a1 alternative splicing switch in a transgenic knock-in mouse model. Matrix Biol. 2012;31:214-26.