The Matrix Letter

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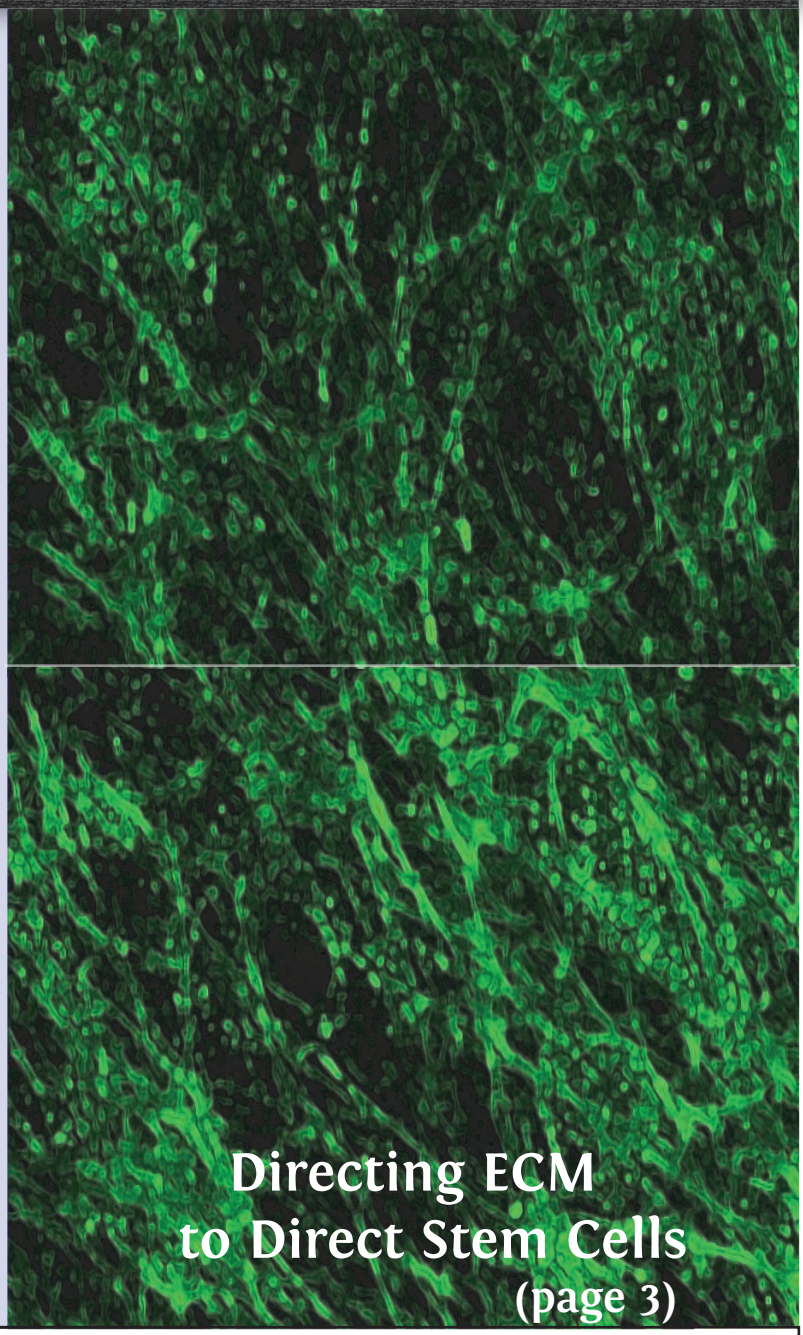

Directing ECM to Direct Stem Cells

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2014 Meeting Site Announced: Cleveland

ASMB is pleased to announce that the 7th Biennial meeting will be held in Cleveland, Ohio at the Marriott Key Center from **October 12-15.**

This prime downtown location is close to numerous destination restaurants, cafes, bars, specialty boutiques and entertainment. Conveniently located for walking or public transportation, the Marriott is in Public Square and near the Westside Market, major sporting venues and the Rock N Roll Hall of Fame.

Major cultural venues such as the world-renowned Cleveland Museum of Art and the Cleveland Orchestra at Severance Hall are a short bus/cab ride away. Suneel Apte and the conference committee are busy preparing a comprehensive program of outstanding speakers and sessions. Save the date now and look for more information about the meeting and fun things to do in Cleveland on the ASMB website.

In addition to providing a vibrant site and active academic center for the meeting, additional concerns of the selection committee were focused on providing an accessible meeting. The central location of Cleveland provides an easy to reach and affordable destination from many research centers on the east coast and the midwest.

The timing of the meeting in Early October will even provide intrepid attendees the option to drive. This promises to be a productive and memorable meeting, and possibly one of our largest to date.

Registration and abstract submission for the meeting will open in the spring of 2014, accesible through the ASMB website (www.asmb.net).

A call for Special Interest Groups has also gone out, and details can be found in this edition of the Matrix Letter (Matrix Interactions, page 5).

We look forward to seeing you in Cleveland!

Protein Kinase A, Nitric Oxide and Atherosclerosis: Is the Answer in the Basement?

Arif Yurdagul & Wayne Orr
LSU Health Shreveport, Division of Research Pathology

Atherosclerosis, while once regarded as primarily a fibrotic disease, involves a complex inflammatory response as leukocytes target to areas of lipoprotein accumulation[1]. Changes in extracellular matrix composition in early lesions contribute to this inflammatory response by altering cell phenotype, suggesting a role for matrix remodeling in both plaque structure and phenotypic modulation [2-4]. Remodeling of the native subendothelial basement membrane (collagen IV, and laminin-8/10) into a fibronectin rich matrix promotes a proinflammatory phenotype stimulating leukocyte homing [2]. Matrix composition can similarly affect monocyte and smooth muscle phenotype in the plaque to promote inflammation [3-5]. Multiple studies demonstrate that limiting fibronectin deposition reduces inflammation and prevents atherosclerotic plaque formation [6, 7]. However, the precise molecular mechanisms regulating these matrix-specific responses are only beginning to be elucidated. Our laboratory studies the mechanisms by which matrix remodeling affects plaque inflammation with particular interest in mechanisms of endothelial cell activation.

Early in atherosclerosis, hemodynamic and systemic factors activate the endothelium, characterized by increased endothelial cell adhesion molecule expression, increased endothelial cell permeability, and decreased nitric oxide (NO) bioavailability. We have previously shown that the subendothelial matrix regulates all facets of endothelial cell activation due to matrix-specific integrin signaling [8]. Specifically, shear stress induced integrin signaling modulates the endothelial cell responses to shear. Adhesion to a fibronectin rich matrix exaggerates endothelial cell activation while basement membrane proteins maintain quiescence [2, 8, 9]. Our work points to a critical role for p21 activated kinase (PAK) in regulating the response to shear stress, becoming activated when cells are attached to fibronectin (both in vitro and in vivo) [8-10]. Basement membrane proteins limit PAK activation through protein kinase A dependent NO production [8-10]. NO accomplishes this through protein kinase G dependent PAK phosphorylation on an inhibitory site preventing PAK translocation to the membrane and limiting its capacity to induce inflammation [8]. Our current investigations focus on how basement membrane proteins activate protein kinase A dependent nitric oxide production, how integrin-specific signals lead to inflammation, and how the extracellular matrix regulates the response to other atherogenic factors.

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[2] Orr AW, Sanders JM, Bevard M, Coleman E, Sarembock IJ, Schwartz MA. The subendothelial extracellular matrix modulates NF-kappaB activation by flow: a potential role in atherosclerosis. J Cell Biol 2005;169:191-202.

[3] Babaev VR, Porro F, Linton MF, Fazio S, Baralle FE, Muro AF. Absence of regulated splicing of fibronectin EDA exon reduces atherosclerosis in mice. Atherosclerosis 2008;197:534-540.

[4] Orr AW, Hastings NE, Blackman BR, Wamhoff BR. Complex regulation and function of the inflammatory smooth muscle cell phenotype in atherosclerosis. J Vasc Res 2010;47:168-180.

[5] Orr AW, Lee MY, Lemmon JA, Yurdagul A, Jr., Gomez MF, Bortz PD, et al. Molecular mechanisms of collagen isotype-specific modulation of smooth muscle cell phenotype. Arterioscler Thromb Vasc Biol 2009;29:225-231.

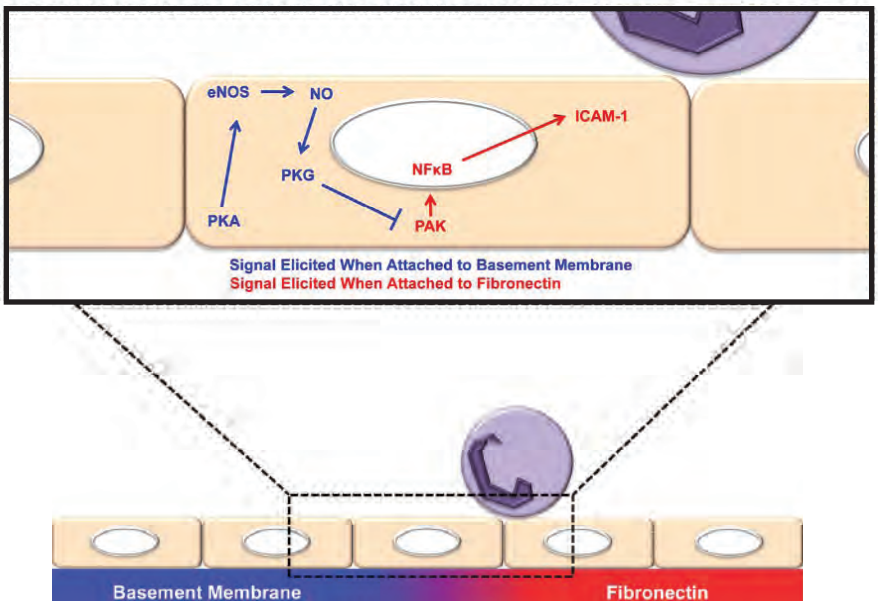
[6] Chiang HY, Korshunov VA, Serour A, Shi F, Sottile J. Fibronectin is an important regulator of flow-induced vascular remodeling. Arterioscler Thromb Vasc Biol 2009;29:1074-1079.

[7] Rohwedder I, Montanez E, Beckmann K, Bengtsson E, Duner P, Nilsson J, et al. Plasma fibronectin deficiency impedes atherosclerosis progression and fibrous cap formation. EMBO Mol Med 2012;4:564-576.

[8] Yurdagul A, Jr., Chen J, Funk SD, Albert P, Kevil CG, Orr AW. Altered nitric oxide production mediates matrix-specific PAK2 and NF-kappaB activation by flow. Mol Biol Cell 2013;24:398-408.

[9] Orr AW, Hahn C, Blackman BR, Schwartz MA. p21-activated kinase signaling regulates oxidant-dependent NF-kappa B activation by flow. Circ Res 2008;103:671-679.

[10] Funk SD, Yurdagul A, Jr., Green JM, Jhaveri KA, Schwartz MA, Orr AW. Matrix-specific protein kinase A signaling regulates p21-activated kinase activation by flow in endothelial cells. Circ Res 2010;106:1394-1403.



Engineering Matrix Properties to Direct Embryonic Stem Cell Differentiation

Hermes Taylor & Adam Engler
UCSD Department of Bioengineering

The Engler lab, part of the Sanford Consortium for Regenerative Medicine on the campus of the University of California, San Diego, is a collaborative team of engineers, biologists, and material scientists that seek to understand how extracellular matrix properties can be used to control stem cell behavior. Our lab has recently been focused on creating microenvironments that mimic the developmental changes of the embryonic niche, e.g. growth factors, extracellular matrix (ECM) proteins and matrix stiffness, to better direct embryonic stem cell (ESC) differentiation and improve current ESC differentiation protocols. In particular, we are interested in how the composition and stiffness of the extracellular matrix can improve the efficiency and maturity of differentiated ESCs.

Matrix Composition

ECM proteins can affect ESC differentiation by several mechanisms. ECM can bind soluble growth factors and regulate their ability to bind to cell receptors. ECM proteins can also directly influence differentiation by binding to integrin receptors and initiating intracellular signaling pathways. Previous work in this area has used single matrix components adsorbed onto glass to study how specific matrix proteins might affect ESC differentiation. Our group hopes to advance this field by studying matrix proteins in the context of an assembled ECM and by accounting for the matrix proteins produced by the ESCs during culture.
We have observed that growth factor cocktails used to induce ectoderm, mesoderm, and definitive endoderm differentiation each cause mouse ESCs to produce different combinations of matrix proteins. One common component of ESC matrix, fibronectin, was required for mouse embryoid bodies to lose pluripotency and differentiate toward any lineage.1 Another component, laminin (LN)-111, was more abundant in endoderm-derived matrix, comparison to the other lineages. We directly tested the affect of LN-111 on ESC differentiation by incorporating the protein into a fibroblast-derived matrix, which normally contains no LN (Fig. 1A). We found that when we plated mouse ESCs on the decellularized fibroblast matrix, the added LN enhanced the efficiency of endoderm induction (Fig.1B) (1). These findings demonstrate that ECM composition can be used to improve ESC differentiation protocols.

Substrate Stiffness

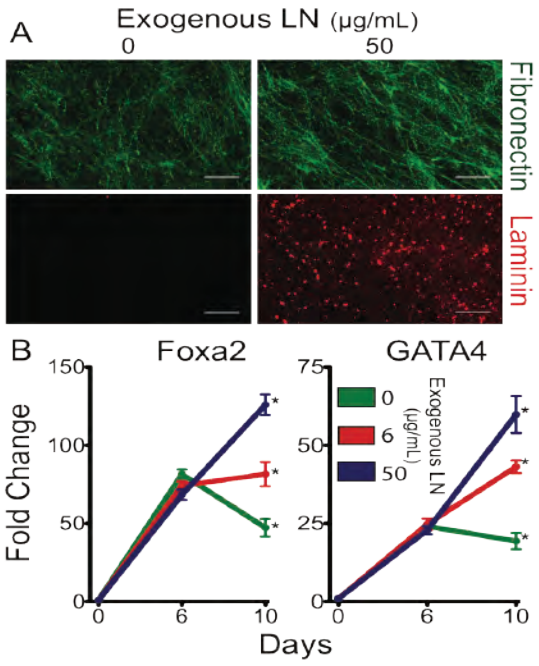
Together with matrix composition, substrate stiffness is another important cue that can guide ESC differentiation. During development, the stiffness of embryonic tissues increases as ESCs differentiate and produce extracellular matrix. The stiffness of a substrate can directly affect ESC differentiation by opening stretch-sensitive ion channels, altering the conformation of focal adhesion proteins, and by activating intracellular signaling pathways (2). Much of the work studying how stem cells respond to substrate stiffness has been done using polymer hydrogels with static mechanical properties. We have contributed to this field by creating dynamically stiffening hydrogels that mimic the stiffening of the developing embryo.
We have measured the stiffness of the developing heart in a chicken embryo model and created a hyaluronic acid hydrogel that dynamically stiffens in a manner similar to the developing heart (3). Embryonic chicken cardiomyocytes were then grown on either the dynamically stiffening hydrogel or on a hydrogel with static mechanical properties. We found that the cells grown on the stiffening hydrogel had higher expression of late markers for cardiomyocyte maturation and were more likely to assemble mature myofibrils, compared with the cells grown on the static substrate. Current work seeks to use this dynamic substrate to increase the maturity of embryonic stem cell derived cardiomyocytes.

1. Taylor-Weiner, H., Schwarzbauer, J. E. & Engler, A. J. Defined Extracellular Matrix Proteins are Necessary for Definitive Endoderm Induction. *In review.*

2. Holle, A. W. & Engler, A. J. More than a feeling: discovering, understanding, and influencing mechanosensing pathways. Current opinion in biotechnology 22, 648–654 (2011).

3. Young, J. L. & Engler, A. J. Hydrogels with time-dependent material properties enhance cardiomyocyte differentiation in vitro. Biomaterials 32, 1002–1009 (2011).

Figure 1. A) Fibroblasts grown with exogenous LN-111 incorporate it into their ECM. B) ESCs grown on decellularized fibroblast ECM exhibited a LN dose-dependent increase in DE marker (Foxa2 and GATA4) expression. Scale Bar = 100 μm.



Matrix Interactions

ASMB News and Announcements in Brief

Call for Nominations

The ASMB awards and nominations committee is currently seeking your nominations for the Junior and Senior Investigator Awards. These awards are an excellent forum to highlight the fantastic achievements of individuals in our field.

Senior Investigator Award:
The Senior Investigator award is presented to an established researcher for outstanding, continued contributions to the field. To be considered for this prestigious award, the nominee must be a current ASMB member, be active in matrix-related research, and be well recognized for making important scientific contributions to matrix biology. To nominate someone for the Senior Investigator Award, please send the CV of the nominee and a letter of support.

Junior Investigator Award:
This award is presented to a newly established, independent investigator who has already made a high-impact finding (or findings) and who shows much promise for continued accomplishments. To be considered for this prestigious award, the nominee must meet the Early Stage Investigator criteria as set forth in the NIH policies (http://grants.nih.gov/grants/new_investigators/index.htm#earlystage), be a current ASMB member, and hold an entry-level faculty appointment (e.g., Instructor, Assistant Professor, or equivalent) at an accredited institution or be an entry-level scientist in industry. To nominate someone for the Junior Investigator Award, please send a letter of support by the sponsor and at least one additional letter of support.

Nominations should be received by email at
asmb@faseb.org
on or before
August 6th, 2013.
Nominations should inclued "Senior Investigator Nomination" or "Junior Investigator Nomination" in the subject line.

Upcoming Events

July 28-August 2, 2013
Vermont Academy, Saxtons River, VT
2013 FASEB Summer Meeting
Matricellular Proteins in Development, Health and Disease.
Co-Chairs: Joanne Murphy-Ullrich, UAB Amy Bradshaw, MUSC
https://secure.faseb.org/faseb/meetings/Summrconf/Programs/11736.pdf

Holderness NH, Gordon Conference:
Biomaterials and Tissue Engineering
http://www.grc.org/programs.aspx?year=2013&program=grs_biomat

August 25-29, 2013
Frankfurt/Main, Germany
Eighth international Conference on Proteoglycans
www.proteoglycans2013.com

October 20-23, 2013
McCracken Country Club, Victor Harbor, South Australia
Matrix Biology Society of Australia & New Zealand Annual Meeting
www.mbsanz.org/2013-,bsanz-conference/welcome

September 8-13, 2013
Madrid, Spain
6th Alpbach Workshop: Coiled-Coils, Collagen& Fibrous proteins
http://shop.bris.ac.uk/browse/product.asp?compid=1&modid=1&catid=579

November 24-27, 2013
Hong Kong Academy of Medicine, Hong Kong, China
9th Pan Pacific Connective Tissue Societies Symposium
www.ppctss2013.org

ISMB Online Upgrade

The ISMB has a new web site! Check it out (see www.ismb.org) for details of upcoming meetings in matrix biology throughout the world, as well as membership, travel grants, prizes and recent issues of the ISMB newsletter.
The new careers section is posting details of current job openings (summary, contact details, deadline). Please send these to the ISMB secretary/treasurer (david.hulmes@ibcp.fr) who will then post these immediately on the site.

Request for Proposals: Special Interest Groups

ASMB Biennical Meeting, October 12-15, 2014 Cleveland Ohio

What are SIGs? Special Interest Groups (SIGs) are an adjunct to, and immediately precede, the formal program for the 2014 ASMB Biennial Meeting. SIGs should be centered on a fairly focused topic, e.g., "3-D culture systems", "ECM diagnostics" "ECM Mineralization. The overall goals of the SIGs are to provide opportunities for investigators working in closely related areas to exchange new data and ideas and to allow students, postdocs, and junior investigators to present their work and receive feedback from leaders in the field. SIG proposals should include the proposed topic title and format and the names and affiliations of the discussion leaders and speakers (if appropriate). *Please send a brief proposal by email to:*

Suneel Apte: ***aptes@ccf.org.*** **Proposal date extended to September 30th, 2013.**

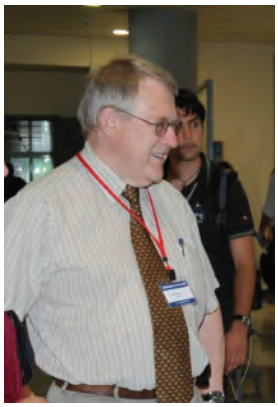
SIG Format, Time & Location : Each SIG will have a 2 hour block. The format of the SIGs is flexible and can be adjusted to fit the goals of the organizers, though typically, the format is similar to other sessions, with 1 (or more) Discussion Leaders and 3-4 speakers. The bulk of presentations should be by those doing the work. ***Space and time has been reserved for only 5 SIGs during the ASMB meeting*** and these will be held on Sunday, October 12, 2014, at the conference hotel, the Marriott Key Center. Sessions will run from 1:00pm – 3:00pm OR from 3:30pm -5:30pm.

In Tribute
Dick Heinegärd

As many of you may already know, Dick Heinegärd, a giant in and much beloved member of the matrix biology field, has passed away. We convey this news with great sadness, while reflecting on the many accomplishments and the continuing legacy of Dr. Heinegärd. Here, many members of our community share fond thoughts and reflections.

Dr. Peter Bruckner, Münster ;

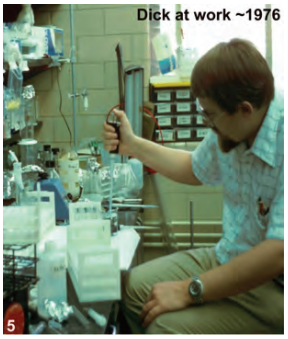
I met Dick Heinegård for the first time in 1984 at a meeting organized by Klaus Kühn, Björn Olsen, and Raul Fleischmayer for the New York Academy of Sciences. Of course, I already knew about Dick's landmark discoveries - together with Vince Hascall - on aggrecan. Although I was under way myself in matrix biology already for several years, I was not really used to raising in my peers such an overwhelming interest in my findings. It was about collagen IX actually being a proteoglycan, something that appeared to be an unthinkable heresy at the time. Needless to say, Koji Kimata already had published exactly this iconoclasm with his JBC paper on PG-Lt which, moreover, turned out to be the same as collagen IX. So, the contribution of Lloyd Vaughan and myself to the advancement of science appeared rater modest to me.



Not to Dick, apparently. He came to my poster and introduced himself. I was awed by the encounter of such a famous colleague and even more by the kind of enthusiastic interest he showed. After about three seconds, however, I realized that I had met a friend rather than a fearsome authority. Dick had this rather rare gift of making patently evident his great respect for every conversation partner without hiding, at the same time, his immense talents. And we stayed friends for many years. I later had the privilege of many scientific communions with Dick, sometimes late into nights at his home or the farm house nearby where he enjoyed his "free" time with his wife Lean. At the time in New York, he insisted in discussing with me the possibilities opened by a proteoglycan-collagen during the whole evening and also the conference dinner. Again, I do not need to mention that we still have only vague ideas about the significance of the dermatan sulphate chains of collagen IX even after thirty years. But Dick already then was thrilled by the union of the major subjects of interest of many matrix biologists, namely his own (proteoglycans) and that of e.g. the conference organizers (collagen). Dick's close familiarity with cartilage where this union takes place so obviously made him curious about our findings. It is easy to say for me that Dick was a scientific visionary and a lot of what we did in Zurich for years after that was stimulated by him.

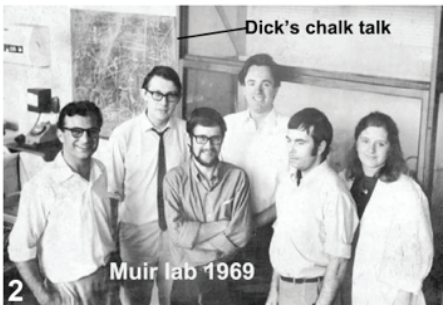
Dr. Bjorn Olson, Boston

"I have been looking for a photograph of Dick Heinegård from one of the many times we were together, but I have been unable to find one that I think is good enough. Good enough in the sense of really reminding us what he was like. So what is the picture of Dick my mind's eye is looking for? I see him as the superb biochemist methodically teasing extracellular matrices apart to reveal their fundamental building blocks. I see him as the speaker at numerous meetings explaining what new components he has discovered and new ideas about how they work, as he did in the opening talk at an April symposium in Boston two years ago. In my mind's eye I see him next to me as we are walking along the beach in Skåne planning the 2009 Gordon Research Conference on Cartilage. I see him and hear him talk, full of ideas and plans, in his office, in his lab and in his apartment in Lund. But dearest of all is my picture of him as the generous host on his farm, in May, taking his American guests on a walk through the forest, seeing, smelling, listening and feeling life return after winter. This is my picture of Dick Heinegård. He was a great extracellular matrix biologist and scientist, but, above all, a real "Mensch" who enriched the life of those he touched."



Vincent Hascall, Cleveland

Dick worked in Helen Muir's lab with Tim Hardingham before I met him in 1971 at the Mucopolysaccharide Gordon Conference. He had arranged to come to Ann Arbor after the conference. I had been told by Dr. Dziewiatkowski (Dr. Jay), who had recruited me to the University of Michigan, that Dick was considering coming to Ann Arbor to do a sabbatical, and that I should impress him. Dick did not seem very impressed, and after showing him our amino acid analyzer with his response "We have a better one", I asked if he was really interested in doing a sabbatical in our lab. With a somewhat surprised look, he said "No, we would like you to come to Lund for a sabbatical." It took about 10 seconds for me to say "Yes", one of the most important decisions I have ever made. A year later my family and I began our Swedish adventure and the establishment of a lifetime friendship for me. It was not always easy at first to get past Dick's reserve, but once there it was delightful, both in and out of the lab. During the year, we met Tim Hardingham and learned of his work on hyaluronan with Helen Muir. This led to a series of experiments that resolved the structure of the cartilage proteoglycan aggregates, introducing the role of the link proteins. Our excitement about the final key experiment went way into the morning hours as we sipped some Danish beer and watched the scintillation counter count out all the vials. Dick returned the sabbatical favor by spending another productive year in my lab in 1976 shortly after I moved to NIH.



My picture of him on the Royal Gorge Bridge during a Colorado vacation (Fig. 3) epitomizes Dick. Dick would look at the extreme depth of the problem from the bridge and still go fishing. It is hard to imagine how many new macromolecules he pulled out of extracellular matrices with his talented colleagues. It was a delight to see his matrix model grow year after year in his wonderful talks, regretfully the last time during his visit to Cleveland last fall. Figure 4 shows the shoulder he always leaned on, his wonderful wife and companion, Lean, whom I was fortunate to get to know in Lund and in Bethesda. Visits to their farm were always a delight, and Dick's persona was always curiosity driving forward to solve the next riddle in his ever expanding matrix research interests. My heart goes out to Lean and their family, and Dick will remain my dear research Brother as long as my memory lasts."

Heinegard, con't.

Stefan Lohmander, Lund:

"We first met in the early 1970ies in Lund, more than 40 years ago. Dick was one of Sven Gardell's PhD students, running liquid chromatography columns, columns and columns, while drinking his Lapsang Souchong tea. I was a green PhD student at the Karolinska Institute coming down to the lab in Lund to learn mucopolysaccharide and later proteoglycan purification and chemistry. We didn't interact much the first years, but once I graduated to the proteoglycan level we published together from 1975 to 2010. It is one of those coincidences that spread like rings on the water that Dick and Vince Hascall then started to work together, first in Lund, then in Bethesda. Dick knew me and my PhD work, and encouraged me to get in touch with Vince and to come over to Bethesda to visit the lab at NIDR where Dick was working in 1976. The Heinegårds, the Hascalls and the Lohmanders then spent a memorable summer vacation together in the Colorado Rocky Mountains. Looking at the old Kodachrome slides brings back smiling memories of us all on midsummer eve, hiking back down from Longs Peak in a snowstorm with thunder and lightning. I guess we passed the test since I was invited to spend a year in Vince's lab in Bethesda, a true game changer in my own career. On returning to Sweden, we soon moved down to Lund, where Dick's support privately and professionally was again critical in building up my own lab and research group in parallel with a clinical training and career. We were young newcomers to Lund, but Dick and his family generously included us among their friends on many visits to their home, island and farm.

We've stayed in touch since then as friends and colleagues for our entire careers, and into 'retirement' as senior professors. Dick was always there, even when traveling, always ready for a discussion, always the generous encyclopedia of matrix knowledge, a true giant in our field. "Ask Dick", were often used words in my discussions with my students, and in time, with their own students. Dick was always curious, always looking around the corner, always thinking forward, and never discarding any piece of information. He was competitive, but would always give you sound advice when asked. His extraordinary global network of friends and collaborators was an asset that we all could tap into when needed. We can't "ask Dick" any longer, but his legacy will live not only in his scientific production, but also in the bright memories of those of us fortunate to have known him."

Suneel Apte, Cleveland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"Dick enjoyed his weekends on his farm in the countryside in peaceful surroundings with his wife Lean. I had the privilege of staying a few days with him at his house in Lund a decade ago (affectionately named "Hotel Heinegård" by his lab, owing to the numerous visitors he hosted there) and spending the weekend with them at their farm. I enjoyed very much the delight that he took in riding his little tractor around (Fig. 6) and strolling the woods ax in hand, looking for something to cut down. Looking back now, I appreciate very much his kindness and generosity to a relative stranger, and the opportunity to have known him not only as a monumental figure in matrix/cartilage biology, but also as a very likeable, unpretentious human being. He was, and remains, an inspiring role model for my generation of matrix biologists."

Bruce Caterson

"I first had the honor and pleasure of meeting Dick in 1976 in Birmingham, Alabama, USA where, ironically, in that same year I also met and befriended for the 2 other infamous "H's" in cartilage matrix biology (i.e. Vince Hascall & Tim Hardingham). From my very first meeting with Dick, I was amazed at his incredible depth of knowledge of basic science, wet lab experimentation and clinical medicine, particularly as they applied to connective tissue research and matrix biology. For the past 37 years I have had the pleasure of meeting up with Dick, usually at numerous meetings in different countries around the world.

At these meetings I would take advantage of his huge knowledge base as 'the Encyclopedia of Matrix Biology' to fearlessly discuss any new/mad thoughts and ideas that I might have but more importantly to find out the very latest of what was going on elsewhere in the ever changing world of matrix biology. Dick was an incredibly hard worker with most of his time in any given day or week being spent in his lab, his office at work, or in his basement at home. For many years, for his holidays, he chose to take up a medical position in the north of Sweden to keep his medical qualifications up to date; i.e. his dedication to medicine & research was second to none and clearly the envy of most of us working in matrix biology. Through the years Dick has received numerous awards in recognition of his achievements and contributions to matrix biology research worldwide. When there were matrix biology meetings in or close to Sweden he very often invited many of the overseas participants to his summer island residence or his farm just outside of Lund. These wonderful 'hospitality extras' that he provided afforded many of us yet another opportunity to pick his brain, meet his wonderful family & friends enjoy matrix biology in a very social & convivial environment. In my opinion, the current knowledge that we have all lost with Dick's sudden and unexpected death is irreplaceable. However, because of his enormous set of achievements and contributions to matrix biology it will be almost impossible for any of us to forget the name Dick Heinegård when we do our research, or just remember wonderful past times. Dick was an incredible person and one whom we all will sorely miss."

Tim Hardingham, Manchester

"I met Dick when I started my first post doc job in Helen Muir's lab at the Kennedy Institute in London. Dick was on a year's study in London with Helen, so we had chance to interact on lots of challenges presented by understanding proteoglycans in cartilage. Dick worked "Swedish hours", arrived about lunch and worked till midnight (or beyond). In the lab he wore clogs, smoked a pipe and drank lapsang souchong tea (very strong). Even then he was a fund of information and a stickler for attention to detail and systematic approach to problems. We continued contact when he was back in Lund and then when he subsequently went to NIH to work with Vince Hascall (and took the lapsang habit with him). I also spent a year with Vince shortly after Dick and the three of us maintained contact and friendship from that time on. In fact as recently as 2006, the three of us shared a holiday in Japan together, with wives and friends. There was a close family of proteoglycan researchers that developed at the time Dick was establishing himself and he was an essential part of that family. There was still rivalry and competition, but there was so much unknown, that sharing information, data and reagents was the norm. Dick was a leader from these early days and he has carried the flag for matrix biology over the past 40 years. It is difficult to think of this field without him there."

Marian Young, Bethesda

"It is with great sadness that we learned about the passing of Dick Heinegård. Since the early days of my research program on extra-cellular matrix and then on small proteoglycans, Dick has been a role model to me for research innovation and excellence. He was a true leader in the field and at the same time devoted to community service and in helping to train and encourage our up and coming matrix scientists. He served on countless committees giving sound and fair advice. He participated enthusiastically in numerous venues for scientific exchange including Gordon Conferences, OARSI, ORS and more. Dick had both solid scientific rigor and a keen sense for important research topics.

Heinegard, con't.

His contributions are too numerous to count having discovered and characterized key matrix components that included the SLRPS, the SIBLINGS and other collagenous and non-collagenous proteins such as COMP, now considered a marker of osteoarthritis. Dick kept clear his focus on bone and cartilage and on the biochemical parameters related to diseases affecting these tissues. His work took basic research findings to important and practical translational applications that impacted diseases caused by mineralized tissue abnormalities. It is not a surprise that Dick was a coveted speaker and discussion leader for professional scientific forums that presented new findings in the field of skeletal biology and pathology. In addition to all of this, Dick enjoyed life. Those of us in the proteoglycan field know how much camaraderie and good times matter to our community and Dick was always in the forefront participating scientifically and socially. Dick, you will dearly be missed!

These thoughts have been compiled by Dr. Renato Iozzo, Editor-in-Chief, and appear in the latest edition of **Matrix Biology.**

We thank Dr. Iozzo for sharing them here with us.

Kate Vogel, Colorado

"In1982 I was a young Assistant Professor at The University of New Mexico. I had taught myself how to study radioactive glycosaminoglycans in fibroblast cultures, but I wanted to actually see proteoglycans. Of course I chose to go to Sweden, the home of proteoglycan research. Thus, thanks to Dick's gracious invitation and a Research Career Development Award from the NIH, my husband and I, along with our two daughters, ages 9 and 12, headed off to Lund for a year. Wow, what a year it was! Our girls went straight into the local schools and quickly learned Swedish. Al did his sabbatical work at the Univ. of Lund Hospital, and I started isolating proteoglycans in Dick's lab. Our first decision was to choose a tissue. Because everybody was working in cartilage at that time I wanted something else. We chose tendon because it was the most fibrous tissue I could think of and because we didn't believe anybody had previously sought tendon proteoglycans. We got some cow feet, dissected out the flexor tendons, and I started learning protein chemistry under Dick's exacting guidance. Every step took so long it was tempting to take shortcuts ("Do I really have to dialyze for three days with changes every 12 hours?") but Dick's unforgettable lesson, in his delightfully colloquial English, was "don't get greedy."

After months of work I had finally produced a small amount of purified small tendon proteoglycan (the molecule later named decorin) at which point, to my horror, Dick insisted that we inject most of this into a rabbit! But it all worked out well. By the end of that year we had characterized the tendon proteoglycans, produced an excellent antiserum, and shown that the core protein of the small proteoglycan interacted with collagen. I was started down a research path that would consume most of my career. For all of this, I thank Dick Heinegård.

During my year in Dick's lab we shared an office and a telephone. Of course nobody called me, but in those days, before answering machines, I quickly learned that when Dick was not there I shouldn't just say "hello", because that would generate long sentences in rapid Swedish that I could never understand. Instead, with exaggerated slow diction I would pick up the telephone and say, "Hello. This is Kathryn Vogel." The surprised caller would usually mumble an apology and hang up. But occasionally I'd take a message and then I could tell Dick that while he was gone, "Stockholm called." I loved telling him that, and I wish the big call from Stockholm had really happened."

Thomas N. Wight, Seattle

"My memory of Dick is someone who was always filled with words of wisdom- a gentle intellectual giant!! The Matrix field has lost one of its pioneers and he will be deeply missed"

Maurizio Pacifici, Philadelphia

"...always helpful and always positive. What a terrible loss for all of us. ….a giant in our field, and I am also sure that his family will appreciate the recognition and appreciation by all of us of his amazing scientific and human qualities"

Virginia Byers Kraus, Durham

"His contributions to our field have been unparalleled. It was a great bounty to be able to experience his magnanimous presence, usual grace and wisdom at OARSI last week. He was always encouraging. For him to tell you "That was clever" and to hear his appreciative laugh was high heartwarming praise. Words cannot express the extent to which he will be missed by us all"

Adele L Boskey, New York

"It is with great sadness that I heard of the passing of Dick Heinegård, he was a great scientist whom I've known for close to 30 years. Dick served as a member of the Scientific Advisory Board of the ICCBMT meeting that I organized in 1985 (I think), and attended all the board meetings that we had, and participated in the program. He later served as a consultant on my grant, providing me with proteoglycans and knockout animals, to use in my study of calcification mechanisms. More than his science, I remember his great sense of humor. He was a great man, and a great scientist, and I am sure we will all miss him."

Heinegard, con't.

These reflections have been compiled by Renato Iozzo, past president of the ASMB, and current Editor-in-chief of *Matrix Biology,* Renato shared these stories, **which will also be published as a memoriam in Matrix Biology.** Here, Renato shares his own memories of Dr. Heinegärd.

Renato Iozzo, Philadelphia.

When I heard the news of Dick's sudden passing, I immediately felt a sense of loss: a giant has left us. Indeed, the definition of "giant" in the field of matrix biology is truly appropriate, as Dick Heinegård possessed prodigious scientific output and strength. Dick was extremely productive and contributed not only to the field of cartilage and bone biology, but also to SLRP biology (his lab cloned and characterized several SLRPs) and to human diseases such osteoporosis and arthritis. One of Dick's best qualities was his uncanny ability to see the "big picture". He was able to connect various interactions of matrix constituents to functional and biological properties that made sense. He was ahead of his times as he was already doing "Systems Biology" of the extracellular matrix before the arrival of supercomputers. His biggest influence to me came from his paper of 1984 with Kate Vogel where they described, for the first time, that the small proteoglycans of tendon, now known as SLRPs, inhibit in vitro fibrillogenesis of both collagens type I and II. This implicated the SLRPs as key regulators of both soft tissues (dermis, interstitial tissue etc.) and hard tissues (cartilage/bones). This seminal observation was subsequently confirmed by several investigators and then by the decorin null mice, which showed abnormal collagen fibrillogenesis in vivo. These observations were confirmed by the biglycan, fibromodulin and lumican deficient mice, which showed abnormal collagen phenotypes, thus validating his observations of more than a decade earlier. In more recent years, Dick has worked on so many aspects of matrix biology that is impossible to summarize them all in a few lines. I should mention that Dick has contributed to the structural and functional characterization of many, now famous, molecules including COMP, osteopontin, fibromodulin, decorin, biglycan, chondroadherin, osteoadherin, PRELP, aggrecan, link protein, and many others. Dick has published over 425 papers with 65 papers in JBC and 36 in BJ, an astonishing output (most of the papers are from his laboratory) equivalent to the productivity required by four full professors to reach tenure!

Anyone who joins our famous Proteoglycan Gordon Research Conference is surprised at our collegiality, friendship and vitality. We are able to have great fun and are proud of our community of scientists. Dick Heinegård was an intrinsic part of this community. I met him at the first PG Gordon in 1984 when I was starting my career at Penn. I was introduced to Dick by Vince Hascall and I thought that I finally joined the 'PG circle of trust". I never left the circle and neither did Dick. He always participated in the scientific program and took part in the interesting and lively discussion. The best personal memories I have of Dick are during the time we spent together talking about science in the green lawn of Proctor Academy, especially during the interminable baseball and cricket games. I wanted to celebrate his life by inviting several of Dick's friend and colleagues to express their feelings and thoughts about him. I like to remember him as a happy, sensitive, mild-mannered and highly-creative human being with a great sense of humor. The photo (Fig. 1) shows Dick at the traditional Thursday evening lobster banquet of the PG Gordon held in 2010. We will greatly miss you.

The Editor's Page

I happened upon the editorship of the Matrix Letter, I believe, simply because I had a vision for what I wanted this newsletter to be, and then conveyed it to the right (or wrong - depending on your viewpoint) people at the ASMB meeting in 2012. Therefore, I suspect there are many among you that could express the following thoughts more eloquently, but I hope you will bear with me. My hope is that simple truths will - in life as in science - act to prove themselves regardless of authorship.

In this issue, we've dedicated space to remembering the contributions of Dr. Heinegärd as a matrix biologist, as a scientist, and as a person. The many thoughts expressed here were compiled by Renato Iozzo. His thoughts are composed in the column opposite this one. Those of my coeditor, Dr. Marian Young, appear on page 6-7. Regardless of whether one actually knew Dr. Heinegärd, it becomes easy to reflect on what it means to be part of the community that is ASMB, how Dr. Heinegärd could so intimately impact our society, and the greater community of matrix biologists world-wide.

I personally never met Dr. Heinegärd, though I was one of many who followed his work, particularly during my PhD studies in the early 1990s. Assembling this issue, there was the nostalgia that accompanies the memory of how our science has evolved; where we were, what we were thinking as landmark 'revelations' such as those orchestrated by Dr. Heinegärd have changed our most basic understanding of biology. Importantly, one is most impressed by the personal friendships that authors forge during the long voyage of mentorship, collaboration and co-discovery. Although the notion seeded within popular culture is that of the idealistic scientist struggling alone in her (or his) lab, the simple truth couldn't be more different. We move forward as a community, and the loss of the integrating force that accompanies the passing of a luminary can be a terrible blow. One feels the need to reinforce old alliances, to mend those that are broken; to heal.

In the United States, the funding climate faced by our community is creating unprecedented challenges. This will very likely lead to fewer training opportunities, which could well translate to fewer researchers in the future. The little community that is the ASMB becomes all the more valuable in this environment. I would urge all of us to seek out other members to include in our studies. Each and every collaboration, every sharing of a reagent or a model system, every interaction makes us stronger as a society. These activities strengthen the network, bringing labs 'closer' together, and foster a camraderie that is all too frequently lost in larger societies. This represents a key strength of ASMB, and we need to nurture it if we are to move forward, particularly as we bid farewell to those that have integrated us in the past.

Dwayne

Positions Available

Director, Orthopaedic Research Center

The Departments of Biomedical Engineering and Orthopaedic Surgery within the Lerner Research Institute and Orthopaedic and Rheumatologic Institute of the Cleveland Clinic are recruiting for a leadership level research position as Director of the Orthopaedic Research Center in any area of musculoskeletal bioengineering, imaging or biology.

The Cleveland Clinic is consistently rated as one of the top 5 hospitals in the country, and the Department of Orthopaedic Surgery is ranked 3rd nationally by the U.S. News and World Report. Over 65 surgeons, 18 non-operative physicians and 72 physical therapists make up this large and clinically diverse department. The Department of Biomedical Engineering is the largest of eleven highly interactive departments in the Lerner Research Institute, and is the leading department in innovation and translation of its technologies into the clinical arena. The Director of the Orthopaedic Research Center will have the exciting opportunity to facilitate and build upon the existing multidisciplinary research and teaching programs in orthopaedic science that exist within and across these two vibrant departments.

We are seeking a full time research and leadership commitment from individuals holding an MD and/or PhD degrees. Recruitment resources and salary will be commensurate with qualifications and scope of responsibilities. Academic title will be at the Associate or Full Professor level in the Cleveland Clinic Lerner College of Medicine, with joint appointment in the Lerner Research Institute and Orthopaedic and Rheumatologic Institute. The successful candidate will have a demonstrated track-record in securing peer-reviewed federal funding as Principal Investigator. She/he will be expected to build a center of excellence, internationally recognized for its strong basic and translational research and academic reputation.

A substantial recruitment package is offered, comprising:

1. An endowed chair
2. Generous start-up funding
3. Executive level administrative support
4. Executive office and conference room located within Lerner Research Institute
5. Three additional recruitments for faculty level positions

Interested candidates should submit a letter of interest and CV to both:

Richard D. Parker, MD
Chairman, Department of Orthopaedic Surgery
Orthopaedic Rheumatologic Institute
Cleveland Clinic Foundation
9500 Euclid Avenue
Desk A-41
Cleveland, Ohio 44195
parkerr@ccf.org

D. Geoffrey Vince, PhD.
Chairman, Department of Biomedical Engineering
Lerner Research Institute
Cleveland Clinic Foundation
9500 Euclid Avenue
Desk ND-20
Cleveland, Ohio 44195
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Orthopaedic and Rheumatologic Institute
http://my.clevelandclinic.org/orthopaedics-rheumatology/default.aspx
Lerner Research Institute
http://www.lerner.ccf.org/
Department of Biomedical Engineering
http://www.lerner.ccf.org/bme/

Postdoctoral Fellow

Mechanisms Contributing to Metastasies of Breast Cancer Cells

Mount Sinai Medical Center
Icahn School of Medicine at Mount Sinai
New York, NY, United States

The lab is interested in understanding the mechanisms that contribute to metastases of breast cancer cells. Specifically we are interested in understanding how breast cancer cells regulate anchorage-independent survival to overcome anoikis, or cell death that results from loss of appropriate extracellular matrix cues. In contrast to normal epithelial cells, which are unable to survive deprivation of matrix signals that help maintain normal tissue architecture, tumor cells are able to survive in altered matrix environments, thereby promoting their dissemination and colonization of distant metastatic sites. We are using genomic and screen-based approaches to develop a comprehensive picture of the molecules and pathways that regulate oncogene-driven anoikis resistance. Our high throughput screen for novel anoikis regulators identified several candidates that are currently being evaluated as potential therapeutic targets for specific breast cancer subtypes. The post-doctoral fellow/staff scientist will develop projects to elucidate the mechanistic basis for regulation of anoikis resistance by these candidates and to evaluate the ability of these candidates to regulate metastases in breast cancer models.

Prerequisites: M.D. and/or Ph.D. with clinical or research experience in the fields of oncology, cancer biology or cancer genetics. Individuals with mouse model experience are particularly encouraged to apply.

PLease submit cover letter and resume/CV to HIRAMSSM@gmail.com

Save the Date