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ASMB Newsletter

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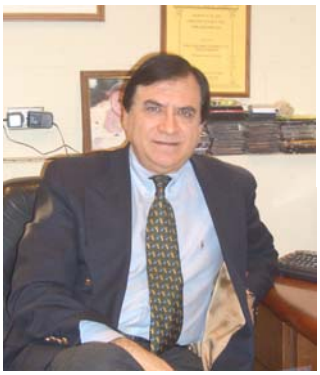
President's Letter


Renato Iozzo

Dear Fellow Matrix Biologists,

During the first 100 days of the new year, we have accomplished a number of goals for the society related to the organization of next meeting and in expanding our membership and reach.

First, with input of the council, we have finalized the dates and the location for our 2008 meeting. The ASMB biennial national meeting will be held at the beautiful Manchester Grand Hyatt in San Diego, California, December 7–11, 2008. Please mark your calendar.

Second, we have formed the Program Committee for the 2008 meeting, which will be comprised of the following colleagues:

Bill Parks (Chair)
Jaime Fitzgerald
Karen Lyons
Ambra Pozzi
Joanne Murphy-Urlich
Ralph Sanderson
Marian Young
Peter Yurchenco
Don Senger (He will be responsible for organizing the Special Interest Groups, SIGs).
Renato Iozzo (ex officio)

The goals of this committee are to organize the various sessions (we will follow the style and template of the 2006 Nashville meeting), submit grants to the NIH and various foundations, contact various companies for support, identify the most suitable speakers and formalize a preliminary program. Thus, I would kindly ask you to submit names and nominations for junior and senior speakers. Please send the nomination to Bill Parks (parksw@u.washington.edu) and Don Senger (dsenger@caregroup.harvard.edu) for the regular sessions and SIGs, respectively.

Another interesting aspect of the 2008 meeting is that we will have the active participation of the International Society of Matrix Biology (ISMB) and thus a session will be organized together with the input of and nominations from the ISMB council and President. Jamie Fitzgerald, who is on the ISMB council and our program committee, provides a link between our societies and will be directly involved in organizing this joint session.

I am pleased to report to you that we have a record number of membership renewals. This is very important because there is a tendency of not renewing the ASMB membership in the year in which there is no meeting. However, there remains a number of members who have not yet renewed their membership. Please, RENEW NOW! Everything can be easily done online by going to http://www.asmb.net.

Last year, we contracted with FASEB to oversee the administration of ASMB. Ann Link was our Executive Director located in the FASEB organization in Bethesda and she has moved on to another position. Ann did a great job for the Society, and we wish nothing but success in her new career. Delores Francis of FASEB has taken over the job. Delores has a significant experience in the running of various societies of comparable size to the ASMB, and we have enjoyed working with her thus far and we look forward to a continued and productive relationship. If you have questions about ASMB administration or if you just wish to welcome her to our Society, please feel free to write Delores at: asmb@faseb.org.

Grants and Study Sections: What can we do as a society for matrix biology?

Every scientist knows that the success of a grant depends nearly exclusively on who reviews it. In the ASCB newsletter of February 2007, Dr Bruce Alberts stated that

"even the best peer-reviewed system cannot reliably distinguish between a research proposal in the top 10 percent and one in the top 15 percent. Thus,…the careers of outstanding researchers can be terminated through bad luck in a chance selection process-one that resembles a game of Russian roulette" I could not agree more with this view. Interestingly, Dr. Alberts chaired the advisory panel to the NIH that produced the January 2000 report entitled "Recommendations for Change at the NIH's Center for Scientific Review". It is my personal view that in an attempt to improve the study section organization, the system has been damaged and is not working properly. The ambitious goal to broaden the study sections and to target disease states is not a good working model. There is a significant lack of expertise in various study sections that review grants from matrix biologists. By restructuring the composition of the old study sections, the NIH has created a sort of vacuum in which the committee members have little expertise in the field and consequently the best grants might not be funded. In an attempt to prevent funding of mediocre science, the so-called "entitlements" that might develop in a certain study sections, the NIH has generated additional and unforeseen problems. This is particularly true in matrix biology. Previously, basic research in matrix biology was reviewed within panels comprised of others investigators actively involved in the area. Importantly, the reviewers could assess the work proposed within a larger context, that is, how it fits into the big picture. This way of evaluating proposal from matrix biologists no longer exists. All the new study sections have been operating now for nearly three years and it is time for an overall evaluation of their success and failures.

Obviously, the time spent on grant writing by each investigator is exponentially increasing every year to the detriment of performing groundbreaking experiments, following new leads of research or learning new approaches. This subject has been well covered by a recent News Focus entitled Boom and Bust (Science, 316:356-361, 2007).

Indeed, the NIH has realized that there is a problem with the organization and structure of the existing study sections and has launched a program where various groups and representatives of various national societies will meet to discuss these problems and to find alternatives. In the upcoming months there will be several open house meetings at the Natcher Auditorium in Bethesda where only two representatives per society will be allowed to attend. In the initial sessions, I and Checco Ramirez will attend these meetings starting in June 2007 when the "Disease-Based Study Sections" will be discussed and analyzed. Future Open Houses will include other members of the Council. I will give you an update in the fall newsletter.

Other important groups of study sections, related to matrix biology, will be discussed in August and October 2007, including the "Integrated Biological Study Sections" and the "Biomolecular Study Section".

I would urge those of you who share similar concerns and motivations to e-mail me (iozzo@mail.jci.tju.edu) your comments, experiences and possible solutions on how to improve the current situation. Your thoughts will be presented at the NIH-sponsored open houses. Now it's time for action!

Warmest regards to all,

Renato Iozzo
President ASMB

New Vice President/President-elect Selected

William C. Parks received his Ph.D. from the Medical College of Wisconsin in 1982 and did his postdoctoral training in extracellular matrix biology with Dr. Robert Mecham at Washington University School of Medicine in St. Louis. In 1986, Bill joined the faculty at Washington University, eventually becoming Professor of Pediatrics, Medicine, and Cell Biology and Physiology and Director of the Center for Developmental Lung Biology. In 2004, he relocated to the University of Washington in Seattle, where he is Director of the Center for Lung Biology and Professor of Medicine. His research focuses on the function of matrix metalloproteinase in immunity and repair and on the molecular regulation of elastin production during development and disease. Bill has organized several meetings, including the Gordon Research Conference on Elastin and Elastic Tissues (1997), the Gordon Research Conference on Tissue Repair and Regeneration (2003), and, with Linda Sandell and Bob Mecham, the International Conference on the Biology and Pathology of the Extracellular Matrix (2000). Bill has served on several advisory committees, including the NIH Pathobiochemistry Study Section and many for the American Thoracic Society, and he currently chairs the Cell Structure and Metastasis Committee for the American Cancer Society.

Bill has been heavily involved with the American Society for Matrix Biology since its inception. In 2001, when ASMB was started by Paul Bornstein and others, Bill was elected as the Secretary/Treasurer, a position he has held to this day. Thus, Bill has been continually involved in ASMB leadership and growth, giving him the experience and history to help build the society even further.

SAVE THE DATES!
December 7-11, 2008
ASMB National Meeting
Grand Hyatt
San Diego, California

The National Meeting of the America Society for Matrix Biology (ASMB) – Program Chair: Bill Parks, University of Washington, Co-Chairs: Jaime Fitzgerald, Oregon Health Science University, Karen Lyons, University of California – Los Angeles, Joanne Murphy-Ullrich, University of Alabama – Birmingham, Ambra Pozzi, Vanderbilt University, Ralph Sanderson, University of Alabama – Birmingham, Marian Young, National Institute of Dental and Craniofacial Research and Peter Yurchenco, UMDNJ Robert Wood Johnson Medical School. Don Senger, Harvard Medical School (SIG organizer), Renato Iozzo (ex officio), Thomas Jefferson University. Detail information on registration and call for abstracts will be announcement in our next newsletter and on the ASMB website at www.asmb.net.

ASMB Administrator at FASEB

Delores Francis has been with the FASEB Managed Society Services since 1992, and is now serving as an Administrator for the ASMB. She has 15+ years of experience in association management. In addition, Delores provides administrative and management support to four associations – The RNA Society, The Society of Biological Inorganic Society, The Society of Chinese Biosciences in America and the International Society for Interferon and Cytokine Research. She looks forward to working with the ASMB and its governance officials to achieve the goals of the Society

Newsletter Committee solicits input from members

Marian Young

The newsletter editors Marian Young (myoung@dir.nidcr.nih.gov) and Veronique Lefebvre (lefebvv@ccf.org) are seeking input for our next newsletter (August edition). A new feature of the newsletter called "Research Highlights" summarizes recent high impact new findings in the field of matrix biology. Contributions to consider for submission are: meeting announcements, job openings, and recognition of awards. Any item you feel will be of interest to the ASMB membership is welcome and can be sent directly to our e-mail address noted above.

ASMB will be meeting in San Diego in 2008! Watch for further details as the year progresses

2007 ASMB Annual Dues

Your 2007 Annual Dues are NOW past due – You can renew and pay via the ASMB website at www.asmb.net. As members you will receive a discount on the meeting and access to reduce or no cost for other ASMB activities. For 2007, Regular membership is $90 and $50 for Students/Postdoctoral Fellow. We need your continued support in the ASMB and we encourage you to RENEW NOW!

Pezcoller Foundation-AACR Recognizes the Oustanding Achievements of Mina J. Bissell

Bissell Honored for Pioneering Work in Understanding the Role of the Tumor Microenvironment and Three-dimensional Architecture in Cell and Cancer Biology

PHILADELPHIA – Mina J. Bissell, Ph.D., is the recipient of the 2007 Pezcoller Foundation-AACR International Award for Cancer Research for her pioneering work on the relationship between cancer genetics and the three-dimensional structure of cells and tissues. Bissell is Distinguished Scientist in the Life Sciences Division at Lawrence Berkeley National Laboratory and a recognized leader in the study of the extracellular matrix (ECM) – the complex physical and biochemical environment that surrounds living tissues – and how it regulates genes in both normal organs and malignant tumors.

This year marks the tenth anniversary of the award, which recognizes an individual who has made a major scientific discovery in basic or translational cancer research. Bissell will give an award lecture at the AACR Annual Meeting 2007 in Los Angeles, Calif., April 14-18. Her talk, entitled "Phenotype Overrides Genotype in Normal Mammary Gland and Breast Cancer," will be given at 5:30 p.m., Sunday, April 15, in Hall A of the Los Angeles Convention Center. In Bissell's honor, the Pezcoller Foundation will hold an award ceremony in early May in Trento, Italy, where she will receive a cash award of €75,000 and a medallion.

Bissell's work in the last two decades has brought the research community to a closer understanding of how cells function in three-dimensional living tissue as opposed to the two-dimensional culture dish. Her group continues to do pioneering work in this area, and in a recent article in Science her group described a new assay using micropatterns of cells sandwiched between two layers of ECM gels, and showed how mammary cells regulate branching which could be used to understand how breast cancer cells become invasive.

Bissell also serves as a member of the faculty of three graduate groups at the University of California, Berkeley, and a member of Cancer Center at UCSF. She has received numerous recognitions and awards for her scientific achievements including her elections as a Fellow of the American Academy for the Advancement of Science, a *member* of the Institute of Medicine of the National Academy of Sciences, and a member of the American Academy of Arts and Sciences. She has been honored both by the Department of Defense (first Innovator Award) and the Department of Energy (the Lawrence Award and the first Distinguished Fellow in Biosciences) and received honorary doctorates from Pierre and Marie Curie University in Paris and University of Copenhagen. In 1997, Dr. Bissell served as President of the American Society for Cell Biology. A member of the American Association for Cancer Research since 1988, Dr. Bissell served on its Board of Directors from 1999-2001, and received the AACR-G.H.A. Clowes Memorial Award in 1999.

Register now for the Bones and Teeth Gordon Conference

The website for submitting applications to the Bones and Teeth Gordon Research Conference is now open. The conference will be held from July15th-20th, 2007 at the University of New England in Biddeford, Maine. Sessions will cover epigenetics, skeletal development, dental biology, stem cell biology, osteoimmunology, metastatic bone disease, calcium and phosphate metabolism and current therapies for the treatment of bone disorders, all of which are emerging areas of relevance to skeletal homeostasis in health and disease. Please see the B&TGRC website for the program:
http://www.grc.org/programs.aspx?year=2007&program=bones
The conference will also feature poster sessions in the afternoons. A series of short talks selected from the posters will be presented at the end of each session. Small travel awards will be presented to those chosen to present short presentations. If you have any questions, please contact Pamela Gehron Robey, the chair at: probey@dir.nidcr.nih.gov

2007 Collagen Gordon Research Conference

The 2007 Collagen Gordon Research Conference will be held July 22-27, 2007 at Colby-Sawyer College in New London, NH. Conference Chair: David Birk, Co-Chair Leena Bruckner-Tuderman. The Program and online application can be found on the Gordon Conference website using the following link:
http://www.grc.org/programs.aspx?year=2007&program=collagen.

International Conference on Proteoglycans

The 5th International Meeting on Proteoglycans will be held September 16-20, 2007 at the Rio de Janeiro, Brazil is now opened for abstracts. Please visit our website for information and registration: WWW.bioqmed.ufrj.br/pgrio2007

2007 FASEB Summer Research Conference on Thrombospondins and other Matricellular Proteins

The 2007 FASEB SRC on Thrombospondins and other Matricellular Proteins in Tissue Organization and Homeostasis will be held June 16-21, 2007 at the Hilton Tucson El Conquistador Golf and Tennis Resort Tucson, Arizona - Co-Chairs: Jack Lawler, Beth Israel Deaconess Medical Center and Harvard Medical School - Boston, MA

2007 Engineering Conference International

The 2007 ECI, titled Engineering Cell Biology II will be held August 5-8, 2007 at the Massachusetts Institute of Technology, Cambridge, Massachusetts, USA. The Conference Co-Chairs are Linda G. Griffith (Massachusetts Institute of Technology, USA, Massachusetts), Gargi Maheshwari (Merck and Co, USA) and Mark Powers (Cambrex Bio Science, USA). For more information and registration, visit:
www.engconfintl.org/7ak.html

2007 Elastin and Elastic Fiber Protein Gordon Research Conference

The 2007 Gordon Research Conference on Elastin and Elastic Fiber Proteins will be held July 29-Aug 3rd, 2007 at University of New Enland, Biddeford, ME. Conference Chair: Elaine C. Davis, Co-Chair Anthony S. Weiss. The Program and online application can be found on the Gordon Conference website using the following link:
http://www.grc.org/programs.aspx?year=2007&program=elastin

Use The ASMB Web Site www.asmb.net

Website Features

- Information about the organization, including bylaws, officers, membership, etc.
- Announcements--items of interest to matrix biologists
- Information about the ASMB National Meeting
- Employment & Funding Opportunities
- ASMB Newsletter archive
- Directory of members
- Links to members' web sites

ASMB business

- When you log onto the "Members Only" page (login using your email address and password. If you have forgotten your password, contact the ASMB office at **asmb@asmb.net**), you will immediately see your dues payment status and a listing of your journal subscriptions.
- You can pay your dues and subscribe to journals by selecting the "Membership Dues" button.
- The "Update" and "Search" buttons allow you to review and update your own contact information as well as search our member database.

To post information about a job opening or job wanted, send detailed information to our Administrative Assistant: **asmb@asmb.net**

Job opportunities and announcements will also be printed in our Society newsletter.

Don't Forget to Renew!

We had a record number of members last year with 450! Your participation in our Society is the most important contribution you can make to helping increase awareness of research and opportunities in extracellular matrix biology.

With the help of your membership dues, in 2006 we added professional management of the society and provided 15 students and postdoctoral fellows with travel awards to our national meeting.

In the coming year, your dues will be at work to improve our website. Among the improvements will be posting an audio of the Keynote address and the abstracts from the ASMB meeting in Nashville, offering an expanded job board, and making the website compatible with all browsers. We urge you to pay your dues so we can continue to add programs that benefit matrix biology.

The 2007 Annual Dues can be paid any time via the ASMB website: http://www.asmb.net/

Alternatively, checks can be sent to the administrative office: ASMB, 9650 Rockville Pike, Bethesda, MD 20814.

Advantages of Membership:

- Membership and recognition in an emerging, important scientific discipline
- A two-year membership rate that is significantly less expensive per year than the one-year rate
- For two-year renewals, a significant discount on the registration fee for the 2008 ASMB National Meeting in San Diego
- Participation in meeting planning and abstract review
- A Newsletter containing information about Society activities

Access to the "Members only" web material where you can search the membership list, the meeting abstracts published in Matrix Biology and other interesting information relating to matrix biology.

Summary of 2007 Meetings of Interest to Matrix Biologist

Osteogenesis Imperfecta Society
The 16th Biennial National Conference on Osteogenesis Imperfecta
Aug 1-3, 2008 Crystal City, VA

American Society of Bone and Mineral Research (ASBMR)
Sept 16-19, Honolulu, HI

V International Meeting on Proteoglycans
Sept. 16-20, Rio de Janeiro, Brazil

Orthopedic Research Society (ORS)
6th Combined Meeting of the Orthopaedic Research Societies
Oct 20-24, 2007, Honolulu, HI

7th Pan Pacific Connective Tissue Societies
Oct 28-Nov 1, Cairns, Australia

American Heart Association (AHA)
Nov 4-7, Orlando, FL

World conference on Osteoarthritis
Dec 6-9, Miami Beach, FL

2007 Gordon Research Conferences

http://www.grc.uri.edu/07sched.htm

Bones and Teeth
July 15-20, University of New England, ME

Cartilage Biology and Pathology
Mar 4-9, Ventura, CA

Cell Contact and Adhesion
May 27-Jun 1, Il Ciocco , Italy

Collagen
July 22-27, Colby Sawyer, New London, NH

Elastin and Elastic Fiber Proteins
July 29-Aug 3, University of New England, ME

Fibronectin, Integrins, and Related Molecules
April 22-27, Lucca (Barga) Italy

Glycobiology
Mar 4-9, Four Points Sheraton, Ventura, CA

Matrix Metalloproteinases
Jun 3-8, Lucca (Barga) Italy o

Small Integrin Binding Proteins
Aug 5-10, University of New England, ME

Don't miss this important and outstanding conference!

5th International Conference on Proteoglycans

Proteoglycans at the beginning of the 21st century
Hotel ClubMed Rio das Pedras-Mangaratiba
Rio de Janeiro-Brazil

September 16-20, 2007

Laboratório de Tecido Conjuntivo
Instituto de Bioquímica Médica - Programa de Glicobiologia e
Hospital Universitário - Universidade Federal do Rio de Janeiro

It is our great pleasure to extend you an invitation to participate in the 5th International Conference on Proteoglycans – "Proteoglycans at the beginning of the 21st century" (September 16 – 20, 2007), which will be held in Club Med Rio das Pedras-Mangaratiba, Rio de Janeiro. Mangaratiba at the Rio de Janeiro coast will provide us a relaxed atmosphere to talk about recent findings on proteoglycans. We are planning talks by investigators who have made important contributions for the understanding of molecular and cellular aspects of proteoglycans dynamics in physiological and pathological phenomena. Scientific sessions will cover diverse themes, including biosynthesis, structure, signaling, development, diseases, animal models and therapeutics. We will also have poster sections for all participants and organized informal speaker/student contacts when young investigators will have the opportunity to discuss their work with foreign scientists.

Mauro S.G. Pavão, PhD and Paulo A.S.Mourão, PhD
Meeting Organizers

FOR MORE INFORMATION:
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Rio de Janeiro, RJ21941-590
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Fax: +55-21-2562-2090
E-mail: mpavao@hucff.ufrj.br

Online registration is open now
on the conference website: www.bioqmed.ufrj.br/pgrio2007/index.htm

Job Position Openings

University of Western Ontario – Postdoctoral Position

CIHR Group in Skeletal Development and Remodeling A postdoctoral position to investigate the role of adhesive signaling pathways in controlling growth factor responses in wound healing, fibrosis and/or scleroderma is available. A combination of cell culture and in vivo approaches will be used. Highly motivated individuals with a recent Ph. D. degree and a demonstrated publication record in molecular & cell biology and biochemistry are invited to apply. Applicant must display excellent communication skills, and thrive in a fast-paced, team-oriented environment.
See http://www.cihrskeletal.ca/leask/index.htm
Email: Dr. Andrew Leask andrew.leask@schulich.uwo.ca

McGill University, Montreal, Canada – Postdoctoral Position

Various exciting projects are available in the lab to study structural and functional aspects of extracellular matrix components involved in genetic disorders of the cardiovascular and skeletal system. The projects focus on components of the microfibril/elastic fiber system including fibrillins and fibulins. A broad spectrum of methods will be involved including recombinant protein production, protein chemistry, proteomics approaches, immunological methods and gene targeting experiments in mice. For further information, please see lab website. Qualifications: Applicants are expected to hold a PhD in an area related to extracellular matrix biology and to have an excellent academic record. Expertise in protein chemistry, mass spectrometry, recombinant protein expression, or animal handling is highly advantageous. Candidates should send by email a cover letter, complete curriculum vitae and the names of two references. Contact Information: Dr. Dieter Reinhardt, Associate Professor, Canada Research Chair, McGill University, Department of Anatomy and Cell Biology, 3640 University Street Montreal, Quebec H3A 2B2, Canada - Phone: (514) 398-4243 Fax: (514) 398-5047. E-mail:dieter.reinhardt@mcgill.ca Web Address: http://www.medicine.mcgill.ca/anatomy/reinhardt/

University of Toronto - Postdoctoral Position

A postdoctoral position is available to study the role of collagen receptors as novel targets to lower the breast cancer risk associated with high mammographic density. Based on previous findings, tissue culture and mouse models will be employed to functionally assess tyrosine kinase signaling of normal and breast cancer cells within the context of the tissue microenvironment. Prior experience with relevant molecular and cell biology techniques as well as animal handling is highly desirable. Additional qualifications include a strong publication track record, good communication skills and superior work ethics.
The position is available in the Dr Wolfgang Vogel's laboratory at the Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto. The University Campus is the core of the most research-intense area in Canada, offering a highly stimulating academic environment.
Please send your curriculum vitae and contact information of three referees to:
w.vogel@utoronto.ca

THOMAS JEFFERSON UNIVERSITY
PHILADELPHIA, PA

POSTDOCTORAL POSITION IN PROTEOGLYCAN RESEARCH, CANCER AND ANGIOGENESIS

A postdoctoral position is available to investigate the biology of perlecan and endorepellin in vertebrate vascular development and tumor angiogenesis. The candidate will join a multi-disciplinary team of researchers involved in investigating the molecular mechanisms through which perlecan and its angiostatic, C-terminal fragment endorepellin affect the development of new blood vessels both in vitro and in vivo (J. Cell Biol. 166:97-109, 2004; J. Biol. Chem. 280:32468-32479, 2005; Nature Rev. Mol. Cell. Biol. 6:646-656, 2005; J. Natl. Cancer Inst. 15: 1634-1646, 2006; Blood 109: 3745-3749, 2007)).

Requirements include a Ph.D. or an M.D./Ph.D. in biochemistry or cell biology. A molecular biology background is highly desirable. Send resume and three letters of reference to:

Renato V. Iozzo, M.D.
Department of Pathology, Anatomy & Cell Biology
Thomas Jefferson University
1020 Locust Street, Room 249 JAH
Philadelphia, PA 19107-6799, U.S.A.
Fax (215) 923-7969
Email: Iozzo@mail.jci.tju.edu

Thomas Jefferson University is an equal opportunity employer.

Funding Opportunities for the Matrix Biologist

There are several foundations that offer funding for biomedical research. Examine each site to identify the particular area of science each foundation funds. Some of the web sites listing funding foundations can be found at:

- http://fconline.fdncenter.org/
- http://www.srainternational.org/newweb/grantsweb/index.cfm?GrantsWebID=106&TitleID=106&SubTitleID=1&GroupID=1&SubGroupID=1
- http://dir.yahoo.com/Health/Medicine/Organizations/Research_Foundations/
- http://www2.lib.udel.edu/subj/foce/resguide/found.htm

A selection of current NIH funding opportunities that should be of interest to matrix biologists in diverse areas:

PAS-07-196, NINDS, 01/05/2007- 07/06/2007
Understanding and Preventing Brain Tumor Dispersal (R01)

PAS-06-201, NINDS, 05/02/2006 - 07/02/2007
Understanding and Preventing Brain Tumor Dispersal (R21)

PA-07-125, NIAMS, 01/05/2007 - 01/03/2008
Muscular Dystrophy: Pathogenesis and Therapies (R01)

PA-06-450, NIAMS, 06/09/2006 - 11/02/2007
Joint Degeneration: Mouse Models (R21)

PA-06-242, NIA, 05/02/2006 - 03/02/2009
Aging Musculoskeletal and Skin Extracellular Matrix (R21)

PA-07-012, NIDDK, 01/05/2007 - 07/06/2008
Animal Models of NIDDK Relevant Diseases (R01)

PA-06-407, NHLBI, 05/10/2006 - 07/02/2008
Directed Stem Cell Differentiation for Cell-Based Therapies for Heart, Lung, and Blood, and Aging Diseases (R21)

PA-07-165, NHLBI, 01/05/2007 -12/31/2009
Pathogenesis And Treatment Of Lymphedema And Lymphatic Diseases (R01)

PA-07-026, NIDDK, 01/02/2007 - 05/02/2009
Developmental Biology and Regeneration of the Liver (R01)

PAR-06-504, NIBIB, 08/20/2006 - 05/21/2009
Enabling Technologies for Tissue Engineering and Regenerative Medicine (R01)

Research Highlights in Matrix Biology

Defects in Proteins Involved in Prolyl 3-Hydroxylation of Collagen Cause Severe Recessive Osteogenesis Imperfecta

Scientists led by Dr. Joan Marini, M.D., Ph.D. at the National Institutes of Health recently identified mutations in two genes responsible for previously unexplained lethal/severe recessive forms of osteogenesis imoperfecta. The discoveries appeared in the recent issues of New England Journal of Medicine (Barnes, Chang, Morello et al., N Engl J Med. 2006 Dec 28;355:2757-64) and Nature Genetics (Cabral, Chang et al., Nat Genet. 2007 Mar;39(3):359-65).

Osteogenesis imperfecta is a genetic bone dysplasia with an incidence of 1 in 15-20,000 births. The disease severity varies from lethality at birth to individuals with severe, moderate or mild forms of this condition whose bones are fragile and susceptible to fracture (Marini 2004. Nelson's Textbook of Pediatrics (Behrman, Kliegman, Jensen, Eds.). pp 2336-2338). Most cases of OI are caused by dominant mutations in either of the two genes coding for type I collagen. However, 10 - 15% of OI patients do not have a mutation in type I collagen. A recessive form of OI was first postulated by David Sillence in his 1979 classification paper (Sillence et al., J Med Genet 1979; 16:101-116) but the etio logy of this form had not been identified. Marini had hypothesized that cases of severe or lethal OI with biochemically abnormal (overmodified) collagen but without a COL1A1 or COL1A2 mutation would be caused by defects in a molecule that interacted with collagen.

The role of CRTAP in bone development was realized when a Crtap (cartilage associated protein) knockout mouse was developed by Roy Morello, Ph.D., and colleagues (Morello et al., Cell. 2006; 127:291-304)at Baylor College of Medicine. Loss of function of Crtap caused defective osteoid formation and severe osteoporosis in mice. Additionally, Morello found that a moderate form of recessive osteogenesis imperfecta, previously described in an isolated First Nations population in Quebec and designated as type VII OI (Ward et al., Bone 2002; 31:12-8.), was due to a hypomorphic CRTAP mutation. The connection of this protein to type I collagen was revealed when Vranka and colleagues (Vranka et al., J Biol Chem. 2004; 279:23615-21) at Shriners Hospital for Children in Oregon showed that CRTAP forms a complex with prolyl 3-hydroxylase 1 (P3H1), encoded by LEPRE1, and cyclophylin B in the ER. In this complex, P3H1 has enzyme activity, verified in vitro, while CRTAP is apparently a helper protein. The complex modifies the single Pro986 residue in the α1 chain of both types I and II collagen.

Marini's team screened tissue samples from 10 patients with severe/lethal bone dysplasia, collagen overmodification and no COL1A1 or COL1A2 mutation, for CRTAP and LEPRE1 mRNA levels using real-time RT-PCR. They found severe reduction of CRTAP mRNA in three patients and of LEPRE1 mRNA in the other seven patients. Null mutations were found in both alleles of the CRTAP or LEPRE1 genes, respectively, in these patients. It is worth noting that five out of the seven P3H1-deficient patients share a common mutation and are either West African or African-American of West African descent. Absence of CRTAP or P3H1 was demonstrated by Western blot in Brendan Lee's or Joan Marini's lab, respectively. Tandem mass spectrometry of patient collagen tryptic peptides, performed in David Eyre's group, revealed the absence of prolyl 3-hydroxylation at the unique Pro986 site in the α1(I) chain of type I collagen in these patients.

Defects in the 3-hydroxylation system secondarily increase modification of the collagen helix. Similar to findings in cases of OI with collagen structural defects, patient fibroblast collagen chains were electrophoretically delayed on SDS-Urea-PAGE. A 25-45% increase in collagen helical hydroxylysine residues, as compared to normal collagen, was demonstrated by amino acid chromatography. Collagen synthesized by patient fibroblasts is secreted from cells more slowly than normal, as frequently occurs with overmodified collagen, but the total amount of collagen secreted per cell is increased. These data suggest that the components of the prolyl 3-hydroxylation complex are crucial for folding of type I collagen chains and that the complex may have a chaperone function. Absence of prolyl 3-hydroxylation may also cause abnormal development in other tissues, such as lung or kidney.

These findings also provide important molecular information for families with recessive OI. It is now possible to offer genetic counseling and prenatal diagnosis to families that have lost a child to these previously unexplained forms of osteogenesis imperfecta. Medical professionals interested in referring patients to NIH to be tested for the recessive OI types as well as the classical types of OI may consult the Web site of the NICHD's OI program at http://www.oiprogram.nichd.nih.gov/.