



Quick Cuts

International Proteolysis Society Newsletter

QC3 - October 2002

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Meeting Reports

- 3rd International Symposium on Serpin Biology, Structure and Function, Chicago, June 2nd-5th 2002.

Organized by P. Gettins, S.Olsen and P. Patston, University of Illinois at Chicago.

This Symposium followed highly successful meetings in Chapel Hill, USA (1996) and Cambridge, UK (1999). In the 1996 and 1999 meetings the emphasis was on the mechanism of protease inhibition by serpins, and the nature of the serpin-proteinase complex. With the report of a serpin-proteinase crystal structure in 2000, and the rapidly expanding size of the serpin superfamily (35 serpins in humans, and over 500 members across other species), the emphasis is now on biology. In each model organism, the questions are the same. What is the serpin complement? Where are they expressed? What are their targets? What physiological processes do they control? From presentations given at the Chicago meeting it is becoming clear that each species has a distinct serpin complement and that targets of so-called "inhibitory" serpins are not necessarily proteases.

Highlights of the meeting included the report by J. Whisstock (Monash University, Australia) of the discovery through bioinformatics of serpins in prokaryotes. That prokaryotic serpins do indeed resemble their counterparts in eukaryotes was confirmed by J. Irving (Monash University, Australia) who presented the crystal structure of an inhibitory serpin from the thermophile *Thermobifida fusca*. Talks from S. Pak (Harvard University, USA) on serpins in *C.elegans*, and J.-M. Reichhart (University of Strasbourg, France) on serpins in *Drosophila*, illustrated that serpins are involved in processes as diverse as osmoregulation and innate immunity. R. Moyer (University of Florida, USA) described a poxvirus "inhibitory" serpin involved in viral host range. Mutants of this serpin have a restricted host range but extragenic suppressor mutations that restore host range occur in components of the viral replication machinery, implying that the serpin target in this case is not a protease.

The concept of non-protease serpin targets was further developed by G. Darnell (Queensland Institute of Medical Research, Australia), who described an interaction between the human serpin PAI-2 and retinoblastoma protein, and S. Grigoryev (Penn State University, USA) who discussed the chromatin-condensing properties of the chicken serpin, MENT. T. Dafforn (Cambridge University, UK) presented a "rope-maker's capstan" model that neatly explains the chaperone function of the non-inhibitory serpin Hsp47 in collagen biosynthesis.

Finally, for those interested in serpin pathophysiology in humans (which is where the field started) there was a plethora of talks on mouse knockouts implicating serpins in neuronal function, reproduction, immunity, cancer and angiogenesis. D. Lomas (Cambridge University, UK) described new therapeutic approaches to the treatment of serpin conformational disease, and M. Petitou (Sanofi Research) gave an elegant exposition of the development and efficacy of synthetic heparins as anticoagulants.

Overall the symposium was an outstanding success. We look forward to the next gathering in Australia in 2005.

Report contributed by Phil Bird, Monash University, Australia

- Gordon Research Conference on Proteolytic Enzymes and Their Inhibitors, July 2002

List of topics covered:

Regulated Intramembrane Proteolysis

Bart De Strooper

Synthetic Protease Inhibitors: New Tools and Drug Leads

Scott Thompson

Protease Specificity and Biological Function

Charlie Craik

Structural Basis of Protease Function

Wolfram Bode

Proteases in Cell Cycle and Cell Death

Guy Salvesen

Proteases in the Immune Response and Inflammation

Hal Chapman

Secreted and Membrane-Associated Proteases in Cancer and Endocrine Function

Bonnie Sloane

Keynote Address: Zena Werb - "The Degradation Monologues"

- International Conference on Dipeptidyl Aminopeptidases
Berlin 26-28th September 2002

A new therapeutic for type II diabetes was uppermost in the minds of about 140 registrants at the recent International Conference on Dipeptidyl Aminopeptidases held in Berlin 26-28th September 2002. Most of the leading academic research groups and the pharmaceutical industry were represented at this conference.

Conference convenor Dr. M. Hildebrandt introduced Dipeptidyl Peptidase (DP) IV as the sleeping beauty, discovered in 1966 but widely recognised as a valuable drug target only recently. Dr. I. De Meester explained that despite the specificity of DPIV for the prolyl bond in a penultimate position in small peptides (with few exceptions), this enzyme modifies the biological activity of many substrates *in vitro*. The presentation by the eminent, experienced DPIV enzymologist Dr. R. Mentlein on his latest step forward in understanding the role of DPIV in chemokine biology was greatly appreciated. He showed data on effects of DPIV cleavage upon CXCL11 (I-TAC) signalling. Dr. Z. Zukowska focused the participants' attention to the possible consequences of DPIV inhibition for the peripheral activity of neuropeptide Y. Glucagon-like peptide-1 (GLP-1) is the most relevant *in vivo* substrate with regard to the potential of DPP IV inhibitors in type II diabetes. Analysing glucose tolerance in the DPIV knockout mouse has supported the potential of this peptidase as a drug target in type II diabetes (Marguet et al, 2000, PNAS). Dr. J. Holst highlighted important points concerning GLP-1 biology while Dr. R. Pederson gave the participants an update on the results obtained with DPP IV inhibitors in

animal models of diabetes. The current status of clinical development of DP IV-inhibitors was presented by Dr. H-U. Demuth who at the same time introduced the concept of 'substrate-specific' inhibition of DPIV.

Unexpectedly, the crystal structure of the DPIV dimer was briefly presented by Dr. D. Webb of Syrrx. The overall topology is similar to prolyl oligopeptidase (1qfm) but the propeller domain is larger and protrusions from each domain form dimerisation sites.

A successful panel discussion chaired by the wise pharmacologist and toxicologist Dr. A. Hildebrandt, provided an overview of the 'ideal' characteristics needed for a DPIV inhibitor in order to be a valuable anti-diabetes therapeutic. Interestingly, differing opinions were elicited about whether DPIV inhibitors must be counter-screened on DP2, FAP, DP8 and DP9 to examine specificity. Earlier, a whole session had been devoted to the biology of DPIV-related enzymes.

Many other aspects of DPIV biology were presented among which were the involvement of DPIV in angiogenesis and in immune mechanisms and disorders. Dr. D. Reinhold presented new results on DPIV/CD26 and multiple sclerosis. The emerging role of DPIV expression on capillary endothelium is one of the many interesting aspects covered at this meeting.

The venue of this successful conference was well placed near many restaurants and the tourist centre of Berlin and immediately preceded the Berlin Marathon and Oktoberfest. Professor Shigehiko Mizutami exhorted us to attend the 2003 IPS meeting in picturesque Nagoya. Researchers from the Otto-Von-Guericke University announced that the next DPIV meeting will be in historic Magdeburg, not far from Berlin, in 2004.

Report contributed by Mark D. Gorrell, Sydney, Australia and Ingrid De Meester, Antwerp, Belgium.

Publication of papers from the 2nd IPS meeting

Papers from the 2nd IPS meeting have been published in the July/August IPS highlight issue of *Biological Chemistry* (volume 383, no 7/8). Thanks to Hans Fritz (Munich) for co-ordinating this. The contents are available on line free of charge to institutional subscribers at www.deGruyter.de/journals/bc

Affiliation with *Biological Chemistry*

Following successful discussions by Hans Fritz and Jennifer Rivett with Executive Editors of *Biological Chemistry*, and email consultation with IPS council members, it has been decided that IPS will have a special association with *Biological Chemistry*. This will involve an increase in the number of manuscripts published in the area of proteolysis but not require IPS members to take out a subscription. Full details will be circulated in the next issue of *Quick Cuts*.

3rd International Proteolysis Society meeting

The 3rd General Meeting of the International Proteolysis Society (and the International Conference on Protease Inhibitors) will be held in Nagoya, Japan.

The tentative scientific topics for the IPS meeting (Nov. 10 - 14, 2003) include:

Protease and Inhibitors in Medicine - Cancer, infection, inflammation, thrombosis, hemostasis

Proteases in Reproduction

Membrane-associated proteases

Processing and degradation

Apoptosis

Structure-function relationships

Tissue remodeling and angiogenesis

Plant/insect proteases/inhibitors

Protease pathogens/toxins and immune response

There will be symposia, workshops and postgraduate courses in the meeting. The topics will include intracellular proteases (ubiquitin/proteasome system, endosome-autophagosome-lysosome system, apoptosis), membrane proteases, MMPs and ADAMs, neurodegenerative diseases, and so on. The second circular will be available within the next few months.

Chair:

Shigehiko Mizutani M.D.

Professor and Chairman

Department of Obstetrics and Gynecology,

Nagoya University School of Medicine,

65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.

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Travel awards for members in training

There will be a number of travel awards to enable members in training to attend the 3rd IPS meeting. Details will be announced in the next newsletter.

Other meetings

December 2002

Two symposia at the Annual Biochemical Society Symposium
London, UK December 16-18, 2002

"Proteases and the Regulation of Biological Processes" (3 days)

Organizers: J Saklatvala, Hideaki Nagase, and Guy Salvesen

"Proteasome interactions with viral and cellular proteins" (1 day)

Organizers: Jennifer Rivett and Martin Allday

April 2003

Vth International Proteasome Workshop, Clermont-Ferrand, France, April 27-29, 2003

Organisers: Yves Briand < Yves.BRIAND@univ-bpclermont.fr > and Didier Attaix

September 2003

57th Harden Conference - Proteinase Structure and Function, 9-13 September 2003

St. John's College, Oxford, UK

Organizers: John Deadman, Robin Leatherbarrow, Brian Austen, Chris Southan

<http://www.biochemsoc.org.uk/meetings/programme.cfm?meetno=H57>

September 2003

A one-day satellite Meeting of the 57th Harden Conference

'Design of Inhibitors for Proteolytic Cascades'

GlaxoSmithKline, Stevenage

9 September 2003

Organizers: Augustin Amour, John Deadman, Corinne Kay, David Hayes and Mike Bird.

<http://www.biochemsoc.org.uk/meetings/programme.cfm?meetno=H57>

October 2003

Inaugural International EMT (Epithelial/Mesenchymal transition - which
involves changes in proteinase expression) Conference ~

Cancer-Development-Pathology October 5-8, 2003

Rydges Reef Resort, Port Douglas, North Queensland, Australia

Website: <http://www.magicdatabases.com/emt.html>

October 2003

IXth International Workshop on Molecular and Cellular Biology of
Plasminogen Activation

CAPRI October 19-23, 2003.

Organizing Committee: Francesco Blasi, M. Patrizia Stoppelli, Pia Ragno

(<http://www.conted.uiuc.edu/pa>)

May 2004

International NO Society Meeting, May 23-28, 2004, in Nara, Japan.

There are other relevant meetings planned for 2003. Please send more meeting details to be included in the next issue of *Quick Cuts* and to be added to our web site managed by Christian Sommerhoff (sommerhoff@clinbio.med.uni-muenchen.de)

Membership renewal

Current membership will lapse at the end of 2002. Soon you will be invited to renew your membership!
Dues: \$100 for 2 years from Jan 2003 for full members, \$40 for 2 years for members in training.

Bids for the 4th International Proteolysis Society meeting

We are inviting bids to host the 4th International Proteolysis Society meeting (probably in 2005).
Informal enquiries to Jennifer Rivett (j.rivett@bristol.ac.uk). All prospective organisers should provide a formal case containing information about organisers, cost and proposed location of the meeting for consideration by the IPS council before January 15, 2003.

New book

NEW FROM PORTLAND PRESS

Essays in Biochemistry Volume 38: *Proteases in Biology and Medicine*
Edited by N.M. Hooper, University of Leeds, UK

1 85578 147 6 – Paperback – October 2002 – 200 pages – £19.00

***Proteases in Biology and Medicine* aims to provide a wide-ranging overview of the many and varied roles of proteases in biological systems, to highlight some of the more recent developments in this area and to provide an insight into future research in the field of proteases.**

Aimed at final year undergraduates, early postgraduates and lecturers, this series of short, punchy and well-illustrated articles written by experts in the field is the first book of its kind to deal with so many aspects of proteases at this level.

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Positions - available and wanted

Two postdoctoral positions available at the **James Graham Brown Cancer Center, University of Louisville, Kentucky, USA**. The research studies the roles of genetic and micro-environmental factors in the activities of proteinases which are involved in tumor cell invasion and metastasis in tobacco-related cancers. The projects are integrated components of the Human Tumor Biology Group at the Brown Cancer Center, which addresses cancer cellular and molecular problems to identify novel gene therapy approaches for cancer. Experiences in mammalian cell culture and basic molecular biological techniques are essential. To apply, please send application letter together with curriculum vitae and names of three references to:

Dr. Wolfgang Zacharias, Ph.D., Associate Prof.
Dept of Medicine and Pharmacol. & Toxicol.
James Graham Brown Cancer Center
University of Louisville, Louisville, Kentucky, USA
w0zach01@gwise.louisville.edu

POSTDOCTORAL POSITION available immediately in the ALBERT EINSTEIN COLLEGE OF MEDICINE, NY, to study changes in protein degradation during aging. The selected candidate must have a Doctoral degree in biochemistry/cell biology/molecular biology or a related field. Experience with assays for the study of protein-protein interactions (i.e. yeast 2-hybrid, co-immunoprecipitation, crosslinking, etc.) preferred. Salary is commensurate with qualifications and experience. Visit our website: <http://www.aecom.yu.edu/cuervo> for details regarding this position and our research interest. Send curriculum vitae and the names of three references to: Ana Maria Cuervo, M.D. Ph.D. (amcuervo@aecom.yu.edu).

A **Post-Doctoral/Research Associate position** is immediately available to study the mechanisms of ischemic and oxidant injury to renal tubular epithelial cells. Cell survival and cell death signaling pathways including the role of caspases, Bcl-2 family members and serine/threonine kinases will be studied. A strong background in molecular biology including cloning, construction of expression vectors, transfections in eukaryotic cells, site-directed mutagenesis and preparation of recombinant proteins is highly desirable. An opportunity to interact with other investigators working in the related areas will be available." Interested individuals should e-mail or fax CV and names of three referees to the following address: Dr. GP Kaushal, Associate Professor of Biochemistry and Medicine, Department of Medicine, University of Arkansas for Medical Sciences 4301 W. Markham Street, Little Rock. AR 72205 Email: Kaushalgurp@uams.edu <<mailto:Kaushalgurp@uams.edu>> Phone: (501) 257-5834 Fax: [501] 257-5827. Thanks

Gur P Kaushal, Ph.D. Department of Medicine, Slot #501
University of Arkansas for Medical Sciences 4301 W. Markham Little Rock, AR 72205 Email:
Kaushalgurp@uams.edu Phone: 501-257-5834 Fax: 501-257-5827

I am **LOOKING FOR A POST-DOC POSITION** starting mid 2003 in the Geneva-Lausanne area. I am just about to finish my PhD studies at the lab of Dr Magnus Abrahamson in Lund University, Sweden. My focus has been on cystatins, especially the novel cystatins E, F, G, H, and I. The work has included generation of a transgenic mouse, mammalian, yeast and bacterial cell culture work, gene cloning and sequencing, expression and purification of recombinant proteins, and protein kinetics. I am interested in working in the proteolysis field either with inhibitors or enzymes. Please contact

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Carl-Michael.Nathanson@klinkem.lu.se
Or cm_nathanson@hotmail.com after December 2002

The metalloprotease “Meprin“ in colorectal cancer: Its role in cell migration and tissue invasion.

Previous analyses of tissues from patients with colorectal cancer suggest that meprin contributes to tumour progression. In the current project we will perform functional studies *in vitro*. We will employ different cell culture models of polarized epithelial cells, either transfected with, or endogenously expressing meprin. We will study the modification of cell migration and invasive behaviour of these cells in response to morphogenetic signals provided by hepatocyte growth factor. We will also consider the role of the uPA - plasminogen activation system, which we have recently shown to mediate activation of meprin.

Among the applied techniques will be:

- 3D cell culture in collagen I gel
- Migration assays in transwell culture systems
- Microscopic techniques including confocal laser scanning microscopy
- Biochemical techniques to study polarized sorting of meprin
- Site-directed mutagenesis of meprin
- Transient and stable transfection of cells

The PhD student will work in a small but expanding research group (Head: Erwin E. Sterchi, Ph.D). The project is funded by the Bernese Cancer league, payment will be according to salary guide lines of the Swiss National Foundation.

Interested? Contact:

Daniel Lottaz, MD, PhD
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University of Bern
email: daniel.lottaz@mci.unibe.ch
phone: +41 (0)31 631 3839



Scientist Position

Protease Reagent Development

Who we are

As one of “The 200 Best Small Companies in America” listed in Forbes magazine for 6 of the past 7 years, R&D Systems specializes in research reagents including cytokines and enzymes. To expand our effort in protease reagent development, a scientist position is available immediately.

The position

The successful candidate will become an integral part of a growing team dedicated to the development of protease reagents for research community. The Scientist will be responsible for developing purification procedures and assay methods for new proteases and related factors. In addition, the Scientist will be involved in the design and development of innovative products that include proteins, antibodies, substrates, inhibitors and assays.

Who you are

Qualified applicants should have PhD in Biochemistry or related field with a minimum of 0–5 years of research experience with purification and characterization of proteases and enzymes. Ability to conceive, research, and manage various projects is essential. Communication (oral and written) skills to present and document work are important. Experience with protein refolding is highly desirable.

We offer a competitive salary and benefits package.

Who to contact

Interested candidates should send, email, or fax a cover letter and resume to:

R&D Systems, Inc.
Attn: SCI/92TJ HR Manager
614 McKinley PL NE
Minneapolis, MN 55413

Email: hr@rndsystems.com
Fax: 612-656-4434

Equal Opportunity Employer.



Your newsletter

Thanks to everyone who has contributed to this issue. Please send any information for the next issue of *Quick Cuts* by email to Jennifer Rivett <j.rivett@bristol.ac.uk>. Anticipated circulation of QC4, January/February 2003.

The International Proteolysis Society web site is <http://www.protease.org>