

BIOCHEMISTRY & MOLECULAR BIOLOGY TODAY

NOVEMBER/DECEMBER 2007 NO. 230



Chair's Message

With the Holiday Season having begun this past week with Thanksgiving, it's a good time to thank all of our BMB family for their efforts over the past year in the common pursuit of our mission. I think we would all agree that our Department is better off today than it was at this time last year. At the same time, we have many accomplishments we can proudly cite.

At the individual level, kudos to Werner Braun for his nomination as a Fellow of the American Association for the Advancement of Science, and we congratulate him on this important recognition. It's significant that our department has garnered the majority of these awards at UTMB.

We have also been able to add three new graduate student awards over the last year or so,

for which I must thank the alumni, the students and the generosity of the faculty who contributed to these, as well as the family and friends of the late Mariann Blum for their significant contributions. As a Department in the School of Medicine and the Graduate School, our commitment to improving the support for our students and our dedication to graduate education are providing impetus toward a more institution-wide awareness of pressing needs in this area.

We have also succeeded in our faculty recruitment efforts, and have added valuable new members who bring important new expertise and perspectives to our faculty furthering achievement of our education and research mission. We have also restructured our staff, and are presently addressing our future needs in the areas of



essential IT support. We are also looking for ways to make grant preparation expertise readily available to all of us. It is also my plan to be able to improve on other aspects of our infrastructure to facilitate what we do, so that we may focus on the core activities of our missions in education and research.

On a personal note, please come to our Holiday Celebration on December 15th at the Yacht Club, and do bring your dancing shoes. May the year to come bring Health, Peace and Prosperity to our BMB family and to your own.

regino



Inside this issue:

Graduate Program Notes	2
BCSO Notes	2
Awards and Announcements	3
Featured Abstract by Faculty	9
Faculty Profile	6-7
Publications	8
Administrator's Notes	5
Faculty on the Road	7

Special Items of Interest

- [Faculty Focus—Kevin Rosenblatt, M.D., Ph.D.](#)
- [Dr. Konkel's Research Coordinator's Columns Online](#)
- [Graduate Program News](#)
- [BCSO Notes](#)

Graduate Program News

Congratulations to Raghavendran Kulasegaran Shylini (Gorenstein laboratory) for being awarded the prestigious McLaughlin Pre-doctoral Award. This is a \$25,000 per year award and only 4 new awards were made this year.

Congratulations also to Paul Evans (Liu laboratory) who was selected for the pre-doctoral training position on the Multidisciplinary Training in Cancer Research training grant.

David Saenz (Boldogh laboratory) and Marlene Starr (Saito laboratory) were winners of poster awards at the 11th Annual Forum on Aging. Over 200 people were in attendance; among 73 poster presentations there were only 9 winners.



From left to right: David Saenz, Marlene Starr, Zane Martin Jones, Trung Nguyen, Dr. Ottenbacher, Lichar Dillon, Chris Fry (for Erin Glynn), Bret Howrey, Eugenia Blomstrom, Lena Rippstein



-Debora Botting, Graduate Program Coordinator

BCSO News

CPS Christmas Toy Drive: It's Holiday Season and as every year, the BCSO, with the help of The Galveston County Child Protection Services, will be helping to bring a brighter Christmas to children under their care. Last year, through your generosity, we were able to sponsor toys for two kids and aim to support 3-4 children this year. We encourage you to donate as little or as much as you can to the Toy Drive. If you wish to donate, you could email the BCSO secretary at kegottip@utmb.edu and we will pick up the donations from your lab or office.



The Pioneering Biological Discovery Seminar series' speaker Dr. George Somero gave a stimulating talk on probing the climatic adaptation mechanisms of organisms using gene chips. It was enlightening to learn first hand about the debilitating effects of Global Warming on the lives of these organisms. Dr. Somero's tying together biochemical analysis and organism-level adaptation, along with some beautiful pictures of ocean life, made it a unique seminar for our department.

BCSO's Social Planning Committee made their debut this year with the Halloween Costume party at BMB program secretary Debora Botting's ranch. Perfect weather, a medley of different cuisines, and a life-size bon-fire created a perfect party for family and friends. Click [here](#) for a detailed account of the party by Paul Evans. The BCSO also sponsored the visit to the Houston Rockets vs Phoenix Suns Basketball game at the Toyota Center on Saturday, November 17th.

- Keerthi Gottipati

Awards and Announcements

Dr. Marc Morais was nominated to represent the University of Texas Medical Branch as its candidate for the Pew Scholars Program in the Biomedical Sciences.

Dr. Chunming Liu received a Bridge funding grant from the Charlotte Geyer Foundation that will provide up to \$100,000 for one year.

Paul Evans, an MD/PhD student in Dr. Liu's laboratory, received a Multidisciplinary Training in Cancer Research predoctoral training grant from the Sealy Center for Cancer Cell Biology and National Institutes of Health Grant T32CA117834.

Dr. Olivera Nestic was awarded an **NIH R21** grant entitled: Aquaporins and Neuropathic Pain after Spinal Cord Injury.

BMB In The News

Potential New Therapy for One of the World's Leading Causes of Blindness mediLexicon, Oct. 1, 2007

An inflammatory eye condition that is one of the world's leading causes of blindness could be treated much more effectively and easily thanks to a new discovery at UTMB. The article quotes professors Kota Ramana, senior author of a paper on the discovery published in the [October issue of Investigative Ophthalmology & Visual Science](#), and co-author Satish Srivastava.

BMB Ranking in NIH Funding FY 2006 Awards (as of 9/6/07) NIH Data without Contract Awards

(provided by William New, Associate Dean for Research)

1	JOHNS HOPKINS UNIVERSITY	\$29,286,114
2	HARVARD UNIVERSITY (MEDICAL SCHOOL)	\$20,715,247
3	VANDERBILT UNIVERSITY	\$20,105,206
4	UNIVERSITY OF TEXAS SW MED CTR/DALLAS	\$20,053,239
5	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	\$18,977,079
6	STANFORD UNIVERSITY	\$18,497,203
7	UNIVERSITY OF WASHINGTON	\$17,436,905
8	YALE UNIVERSITY	\$15,396,191
9	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL	\$14,503,872
10	UNIVERSITY OF TEXAS MEDICAL BR GALVESTON	\$12,372,677
11	BOSTON UNIVERSITY MEDICAL CAMPUS	\$12,367,157
12	TUFTS UNIVERSITY BOSTON	\$11,609,553
13	YESHIVA UNIVERSITY	\$10,554,432
14	UNIVERSITY OF MICHIGAN AT ANN ARBOR	\$9,837,833
15	BAYLOR COLLEGE OF MEDICINE	\$9,835,809
16	UNIVERSITY OF MARYLAND BALT PROF SCHOOL	\$9,187,293
17	DUKE UNIVERSITY	\$9,159,386
18	CASE WESTERN RESERVE UNIVERSITY	\$9,014,614
19	UNIV OF MASSACHUSETTS MED SCH WORCESTER	\$8,657,077
20	UNIVERSITY OF MINNESOTA TWIN CITIES	\$8,443,234

Administrator's Notes



Administrative Staff Additions and Changes

We welcome **Stacy Diaz**, who joined BMB as a half-time Administrative Coordinator on October 8. Stacy supports the operation of the Bioinformatics Program and assists Dr. Bruce Luxon, in addition to providing administrative assistance as needed for the Sealy Center for Molecular Medicine and for BMB functions. Stacy's office is in 5.138 MRB and her phone number is 24227. (Stacy is a full-time UTMB staff member who covers two half-time assignments; she is also the coordinator of the McLaughlin Program in the Institute for Human Infections and Immunity.)

A farewell luncheon was held for **Martha Harris**, who retired on October 31. For the present, Martha's position is remaining unfilled while we evaluate the current need for assistance by a full-time Laboratory Support Technician. In the interim, **Steve Hathorn** has agreed to assume the tasks formerly assigned to Martha, and his position has been adjusted to reflect his expanded responsibilities.

We have also created new functional teams for assisting faculty members with financial management of grants and other accounts supporting individual research. On each team, the **Senior Administrative Secretary** assigned to the research group is partnered with an **Account Coordinator**, who is a member of the department's financial staff. The Senior Administrative Secretary provides direct financial operations support for the research group and performs the more routine functions of recording and reporting information on the actual and projected status of accounts. The Account Coordinator performs the more technical accounting and analytical functions and assists with preparing financial reports and resolving non-routine problems.

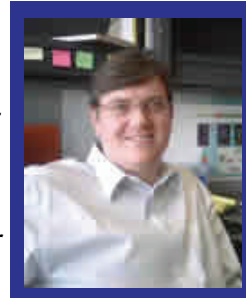
Power Outage in Basic Science and Medical Research Buildings on November 29

The sudden electrical power outage that occurred on November 29 lasted approximately 90 minutes in most of the affected area. The incident provided an opportunity to observe how the emergency electrical system performs when there is a sudden failure of the main system and also helped us become familiar with certain features such as the location and intensity of emergency lighting. We appreciate the assistance of everyone who passed along important information about issues that need to be addressed. We will be following up on certain questions with FOAM and will provide additional information about power emergencies in next month's newsletter. Please send me any questions or concerns about this. And in the meantime, be sure to replace flashlight batteries and make sure flashlights are placed in the designated locations.

Up-coming Visit by State Fire Inspectors

The State fire inspectors will be focused on assessing fire safety in research buildings. The inspectors could arrive at any time, and the dates of their visit will not be announced in advance. It's very important to check all labs *now* to make sure that appropriate fire safety practices are being followed. The Office of Environmental Health and Safety has provided a [checklist](#) to help lab members evaluate their areas. Please contact Steve Stokes in EHS if you have questions about fire safety issues.

Faculty Focus: Kevin P. Rosenblatt, M.D., Ph.D., Associate Professor, BMB



Dr. Rosenblatt graduated cum laude from Tulane University, New Orleans, Louisiana with a double major in Chemistry and Judaic Studies. He then graduated from the Medical Scientist Training Program at UT Southwestern in June of 2000 where he earned both a Graduate degree in the Department of Neuroscience and a Medical degree. His graduate studies required the development of several novel and technically challenging molecular techniques (e.g. in situ, exon-specific, RT-PCR) which lead to a cover article in Neuron During his senior year in medical school, he was awarded the Stembridge Award for Excellence in Pathology for his medical school academic achievements and research accomplishments.

At the NIH in Bethesda, Maryland, Dr. Rosenblatt completed the Anatomic Pathology Residency Training Program along with a Clinical Research Fellowship in Clinical Proteomics within the FDA-NCI Clinical Proteomics Program. During his residency, he changed his research focus from the neurosciences to the discovery of genomic and proteomic biomarkers for the diagnosis and management of cancer.

He was then recruited by the Department of Pathology at the University of Texas Southwestern Medical School as the Associate Director of the Division of Translational Pathology in November 2003. There, he was founder and Co-Director of the UT Southwestern Tissue Repository (UTSTR), a comprehensive tissue bank concentrating on the collection of human clinical samples, and Director of the Clinical proteomics program.

On October 15, 2007, Dr. Rosenblatt began a joint appointment as Associate Professor in the Department of Biochemistry and Molecular Biology and the Department of Internal Medicine at UTMB. He is also a Scientist and Director of Biomarker Development in the Sealy Center for Molecular Medicine; a Project Leader for Biomarker Discovery in the NHLBI Proteomics Center; and a member of the Sealy Center for Cancer Cell Biology.

My main focus of interest is in the discovery and validation of biomarkers and novel drug targets for molecular pathways of disease in animal and cell models and in human biological fluids and tissues. Mostly, I have focused on protein-based biomarkers and molecular targets because proteins are the "workhorses" of cells and tissues--i.e. proteins carry out the majority of the cell signaling and metabolic reactions necessary for normal physiology, and deranged protein networks are responsible for altered metabolism that results in disease. Thus, while studying the mutations of key genes in the genome and how these mutations effect gene expression at the message level is incredibly useful for understanding the molecular basis of many diseases, a knowledge of how protein expression is altered--which proteins, their relative levels, and their altered regulation at the post-translational level--is necessary for a more complete understanding of a disease process.

A cell's proteome (a complete description of protein expression and regulation for a cell) is more complex than its genome: Each protein species derived from an alternative spliceform of a gene or from an alternate post-translational modification, and proteins in complex with with different proteins as a multimeric complex, and indeed proteins that exist in different conformational states, may all exhibit a discrete activity that may yield valuable information; the sum of these possibilities is far greater than the total number of genes in the genome. Because of the vast chemical and structural complexity of the proteome, then, it is important to develop technologies that have reasonable throughput and suitable dynamic range (for example, the dynamic range of protein expression levels may be as high as 10^{11} to 10^{14} in the blood) for protein target discovery. Thus, my group has been engaged in the development of technologies that facilitate protein marker discovery and technologies by which tentative targets can be validated. Many of our initial studies have been directed towards

human fluids and tissues for the direct discovery of human markers and therapeutic targets; these types of studies depend on a close collaboration and interaction with clinicians, chemists, technologists, biologists, informaticists, and statisticians. Therefore, we envision the Sealy Center for Molecular Medicine as an appropriate center of activity for these types of clinically oriented studies.

We have also worked out high-throughput screening methodologies, including phospho-proteomic lysate microarrays, for dissecting cell signaling pathways (e.g. for profiling kinases such as MAPK, and transcriptional activators) that drive signaling in diseased cells, such as cancer cells.

These functional genomic approaches can lead to the selection of druggable candidates and suitable signaling profiles that distinguish one disease sub-classification from another--useful tools in this new era of personalized molecular medicine. Future projects include the design of high-content imaging assays for protein expression- and morphologically-based biomarker and drug target discovery.

Finally, because animal and cell line models are still a useful way to gain insight to human diseases and cellular physiology, we work in collaboration with basic research groups to apply the above methodologies to such models to discern candidates that may be relevant to human disease. We then attempt to translate these findings into human diseased tissues and biological fluids to determine relevance for the human disease correlates. Along these lines, we have been using proteomic and functional genomic techniques to dissect the protein networks driving Klotho protein signaling cascades: Klotho is a novel protein family member that has been implicated in aging/longevity and oxidative stress pathways in mammals. Klotho is a single pass transmembrane protein, expressed in limited tissues, that is released and circulates in the blood and CSF and has potentially far reaching effects on cellular metabolism. Recent efforts and publications have concerned the identification of the Klotho "receptor" and some of the cytoplasmic and nuclear signals of Klotho activity and their biological consequences; we are now engaged in translational projects to determine the role of this protein, if any, in human aging and in human age-related diseases such as Parkinson's Disease and in cancer. Studies such as these may increase our understanding of cancer pathogenesis and neurodegeneration and suggest novel approaches to therapies.

Recent publications from Dr. Rosenblatt

1. Fisher, W.G., Rosenblatt, K.P., Fishman, D.A., Whiteley, G.R., Mikulskis, A., Kuzdzal, S.A., Lopez, M.F., and Garner, H.R. (2007) A robust biomarker discovery pipeline for high-performance mass spectrometry data. *Journal of Bioinformatics and Computational Biology* 5: 1023-1045.
2. Kurosu, H., Choi, M., Ogawa, Y., Dickson, A.S., Goetz, R., Eliseenkova, A.V., Mohammadi, M., Rosenblatt, K.P., Klierer, S.A., and Kuro-o, M. (2007) Tissue-specific expression of β Klotho and fibroblast growth factor receptor isoforms determines metabolic activity of FGF19 and FGF21. *Journal of Biological Chemistry* 282: 26687-26695 (Accelerated Publication; On-Line July 10, 2007).
3. German, D.C., Gurnani, P., Nandi, A., Garner, H.R., Fisher, W.G., Diaz-Arrastia, R., O'Suilleabhain, P., and Rosenblatt, K.P. (2007) Serum biomarkers for Alzheimer's disease: Proteomic identification. *Biomedicine and Pharmacotherapy* 61: 383-389 (On-Line June 18, 2007).
4. Lopez, M.F., Mikulskis, A., Kuzdzal, S., Golenko, E., Petricoin III, E.F., Liotta, L.A., Patton, W.F., Whiteley, G.R., Rosenblatt, K.P., Gurnani, P., Nandi, A., Neill, S., Cullen, S., O'Gorman, M., Sarracino, D., Lynch, C., Johnson, A., McKenzie, W., Fishman, D. (2007) A novel, high-throughput workflow for discovery and identification of serum carrier protein-bound peptide biomarker candidates in ovarian cancer samples. *Clinical Chemistry* 53: 1067-1074 (on-line April 26th, 2007).

Faculty on the Road

Dr. Wlodzimierz Bujalowski traveled to Washington, D.C., to participate in MSFB Study Section, October 10th thru October 12th, 2007.

Dr. Bujalowski was also in Nashville, Tennessee, October 21st, to present a seminar to the Vanderbilt University Chemistry Colloquium.

Dr. Bruce Luxon visited the Mayo Clinic in Jacksonville, FL Oct 4-5th to give an invited talk on "Systems Biology Enabled Discovery of Targets and Biomarkers in Cancer Research".

Dr. John E. Wiktorowicz traveled to Seoul, South Korea to attend the 6th Annual World Congress of the Human Proteome Organization on October 4th, 2007.

Dr. Stanley Watowich was an invited speaker at the 5th Annual Congress of International Drug Discovery Science and Technology: Advances and Challenges toward Major Diseases 2007 in Xian, Chin on November 2-10, 2007. The title of his talk was "Global Grid-computing Initiative to Discover Novel Dengue and Hepatitis C Antivirals."

Dr. John Papaconstantinou's group attended the Nathan Shock Aging Center Conference on Aging "Age-Related Muscle Atrophy: Causes and Mechanisms" October 25th through October 27th in Bandera, Texas. All five attendees presented posters:

Dr. Papaconstantinou: "High-Throughput Liquid Fractionation of Multiple Protein Post-Translational Modifications",

Dr. Chingchuan Hsieh: "Fibroblast Cells from Young and Aged Long-Lived Ames Dwarf Mice Exhibit Resistance to Reactive Oxygen Species (ROS) Generated by Mitochondrial Dysfunction",

Vincent Dimayuga: "Increased Endogenous Oxidation of Resident Endoplasmic Reticulum Proteins, Protein Disulfide Isomerase and BiP, Results in Decreased Chaperone-Related Enzymatic Activities in Aged Mouse Livers",

Eric Bailey: "Age-Related Alterations in Oxidatively Damaged Proteins of Mouse Skeletal Muscle Mitochondrial Electron Transport Chain Complexes",

James Amaning: "A Proteomics Analysis of the Effects of Chronic Hemiparetic Stroke on Troponin T Expression in Human *Vastus Lateralis*".

Dr. Catherine Schein attended the Keck meeting on High Throughput Screening on Nov. 8. in Houston.



To have your travels included in the monthly newsletter, please send the information directly to Lisa Pipper (lpipper@utmb.edu) by the 1st of each month.

BMB Faculty Publications

Acharya, N., A. Brahma, L. Haracska, L. Prakash, and S. Prakash (2007) Mutations in the ubiquitin binding UBZ motif of DNA polymerase h do not impair its function in translesion synthesis during replication. *Mol. Cell. Biol.* 27: 7266-7272.

Gangavarapu, V., S. Prakash, and L. Prakash (2007) Requirement of *RAD52* group genes for postreplication repair of UV-damaged DNA in *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* 27: 7758-7764.

Blastyák, A., L. Pintér, I. Unk, L. Prakash, S. Prakash, and L. Haracska (2007) Yeast Rad5 protein required for postreplication repair has a DNA helicase activity specific for replication fork regression. *Mol. Cell* 28: 167-175.

Choksi KB, Nuss JE, Boylston WH, Rabek JP, Papaconstantinou J. Age-related increases in oxidatively damaged proteins of mouse kidney mitochondrial electron transport chain complexes. *Free Radic Biol Med.* 2007 Nov 15;43(10):1423-38. Epub 2007 Aug 15.

Choksi KB, Roberts LJ 2nd, DeFord JH, Rabek JP, Papaconstantinou J. Lower levels of F2-isoprostanes in serum and livers of long-lived Ames dwarf mice. *Biochem Biophys Res Commun.* 2007 Dec 28;364(4):761-4. Epub 2007 Oct 25.

Nuss JE, Choksi KB, DeFord JH, Papaconstantinou J. Decreased enzyme activities of chaperones PDI and BiP in aged mouse livers. *Biochem Biophys Res Commun.* 2008 Jan 11;365(2):355-61.

Marcinowicz A, Jezewska MJ, Bujalowski W. Multiple Global Conformational States of the Hexameric RepA Helicase of Plasmid RSF1010 with Different ssDNA-Binding Capabilities Are Induced by Different Numbers of Bound Nucleotides. *Analytical Ultracentrifugation and Dynamic Light Scattering Studies.* *J Mol Biol.* 2007 Jun 27;

Jezewska MJ, Bujalowski PJ, Bujalowski W. Interactions of the DNA Polymerase X from African Swine Fever Virus with Gapped DNA Substrates. Quantitative Analysis of Functional Structures of the Formed Complexes. *Biochemistry.* 2007 Nov 13;46(45):12909-12924.

Marcinowicz A, Jezewska MJ, Bujalowski PJ, Bujalowski W. Structure of the Tertiary Complex of the RepA Hexameric Helicase of Plasmid RSF1010 with the ssDNA and Nucleotide Cofactors in Solution. *Biochemistry.* 2007 Nov 20;46(46):13279-13296.

Jezewska MJ, Bujalowski PJ, Bujalowski W. Interactions of the DNA polymerase X of African swine fever virus with double-stranded DNA. Functional structure of the complex. *J Mol Biol.* 2007 Oct 12;373(1):75-95.

N. Garmashova, S. Atasheva, W. Kang,, S.C.Weaver, E. Frolova, and I. Frolov. Analysis of Venezuelan Equine Encephalitis Virus Capsid Protein Function in the Inhibition of Cellular Transcription. *Journal of Virology*, December 2007, p. 13552-13565, Vol. 81, No. 24.

New - ONLINE Version
Research Coordinator's Corner
www.bmb.utmb.edu/department/RCC/

Featured Abstract by BMB Faculty**A ROBUST BIOMARKER DISCOVERY PIPELINE FOR HIGH-PERFORMANCE MASS SPECTROMETRY DATA.**

J Bioinform Comput Biol. 2007 Oct;5(5):1023-45.

Fisher WG, **Rosenblatt KP**, Fishman DA, Whiteley GR, Mikulskis A, Kuzdzal SA, Lopez MF, Tan NC, German DC, Garner HR.

Division of Translational Research, Department of Medicine, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA. Wayne.Fisher@utsouthwestern.edu.

A high-throughput software pipeline for analyzing high-performance mass spectral data sets has been developed to facilitate rapid and accurate biomarker determination. The software exploits the mass precision and resolution of high-performance instrumentation, bypasses peak-finding steps, and instead uses

discrete m/z data points to identify putative biomarkers. The technique is insensitive to peak shape, and works on overlapping and non-Gaussian peaks which can confound peak-finding algorithms. Methods are presented to assess data set quality and the suitability of groups of m/z values that map to peaks as potential biomarkers. The algorithm is demonstrated with serum mass spectra from patients with and without ovarian cancer. Biomarker candidates are identified and ranked by their ability to discriminate between cancer and noncancer conditions. Their discriminating power is tested by classifying unknowns using a simple distance calculation, and a sensitivity of 95.6% and a specificity of 97.1% are obtained. In contrast, the sensitivity of the ovarian cancer blood marker CA125 is ~50% for stage I/II and ~80% for stage III/IV cancers. While the generalizability of these markers is currently unknown, we have demonstrated the ability of our analytical package to extract biomarker candidates from high-performance mass spectral data.