

BIOCHEMISTRY & MOLECULAR BIOLOGY TODAY

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Chair's Message

We are now in that early summer period when we must all take a weekend to review our personal hurricane plans. Not just checking on supplies at the lab and our homes, but more importantly, deciding what we will do in case a category 1 to 3 hurricane heads for Galveston. Above category 3, there really is no choice for most folks living south of Houston, as the storm surge would overtop the Galveston Seawall and put almost everyone's house underwater. Although the number of hurricanes actually hitting Galveston is small (the last big one I remember was Alicia in 1983 -- that was a category 3, and no, I did not evacuate), there is always the chance that **this** summer will bring one to our shore. If it comes off the African coast, there are several days to decide, but if it forms in the Gulf, it can be here in just a day or two. It is also important to remember that the Causeway and the ferries will be closed when the winds top 50 mph. Also to be considered is the situation where you are attending a meeting or on vacation, only to learn that a storm is headed for Galveston. If you are traveling this summer, make arrangements for such situations. So talk it over with your lab colleagues and family, and

make your plan **now**. Our Safety and Emergency Management Committee will be reviewing the Department's emergency plan and may recommend additional actions to take in preparation for the possible arrival of a hurricane.

Do not forget we are interviewing candidates for tenure-track faculty positions, and make every attempt to attend the seminars. In the next couple of weeks we will have two candidates working in the microRNA field. Both candidates will be presenting interesting work in a fairly new field. Please come to these seminars.

On June 27th, we will be hosting our symposium celebrating Wayne Bolen's scientific accomplishments. Outstanding speakers will honor Wayne, and we all look forward to a scientific fest honoring one of our most respected colleagues. Personally, I consider myself privileged to have worked with Wayne over the years. In addition to his ground-breaking research, his commitment to the Department and graduate education account for much of what we have accomplished in



recent years. Please join us on the 27th at 9am in Levin Hall.

Our faculty and alumni are being asked to contribute to funds to establish a number of student awards. This is an important cause and another case where we all benefit from a successful fund-raising effort. Our graduate students are the most important component of our academic lives, touching on both our educational and research missions. As we were told at the last faculty meeting, contributions do not have to be large, but participation by a large proportion of our faculty will send an important message of our commitment to the students now on board, and to others who will decide whether to join us in the future. Please give whatever you are comfortable with. (Yes, I know one should never end a sentence with a preposition).

Enjoy the balmy breezes and slower summer rhythms.

regino

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Special Items of Interest

- Faculty Focus— [Tapas K. Hazra, Ph.D.](#)
- Emergency Weather Information and FirstCall

Graduate Program News

This month, our students have been very busy with defending dissertations, graduating, passing the qualifying exam and winning awards.

Jason Vertrees and Suwei Wang, both of the Hilser laboratory and Sergio Santa Maria, Prakash laboratory, successfully defended their dissertation research and have begun the next stage in their careers.

Ping Liu, Brasier lab, graduated and will be starting his residency in internal medicine

Two of our former students, Scott Larson, Hilser laboratory, and Marsha Tallman, O'Connor laboratory, have completed their medical school education and will begin their residencies this month. Dr. Larson will be a resident in internal medicine at the Mayo Clinic, Rochester and Dr. Tallman in emergency medicine at the Allegheny General Hospital, Philadelphia.

We are so proud of Aishwarya Ravindran, Rajarathnam lab, for being awarded a scholarship from the American Heart Association (AHA). This the very first time such an award is being made to international pre-doctoral students. We also congratulate Austin Elam, Hilser lab, for being awarded the Space Grant Consortium Fellowship.

Congratulations to all our students who have passed their Written and Oral Qualifying Examinations! They are currently being reviewed by the BMB Evaluation Committee, chaired by Dr. Wlodek Bujalowski. The students are: Rayhan Ahmed, Barral lab; Natasha Brooks, Lisa Elferink lab; Daisi Chen, Epstein lab; Vincent Dimayuga, Papaconstantinou lab; Hung Doan, Evers lab; Gabriela Kulp, Jeschke lab; Emilio Reyes-Aldrete, Morais lab; Scott Silva, Evers lab; Marlene Starr, Saito lab; Sai Gandham, Gorenstein lab; and Debashish Sahu, Iwahara lab.

The BMB Graduate Program Review (along with the BMB Departmental Review) is now completed and we would like to thank our faculty, staff and students who worked very hard on the preparations. We were happy to see some of our alumni return to the island to meet with the external review panel: Lavanya Rajagopalan, Scott Larson, Matt Auton and Rodrigo Maillard.

Some of our students led the way with active fundraising for the earthquake victims in China. The fundraising effort was organized by the UTMB Chinese Students and Scholars Association (CSSA). Daisi Chen, BMB student in Dr. Epstein's lab, is the current president of CSSA. Several members of CSSA, including Julie Hou, Brasier lab, helped send emails to different departments and collected donations in different buildings. The donations totaled over \$11,000 and will be used to rebuild schools in the quake zone and help children there continue their education.

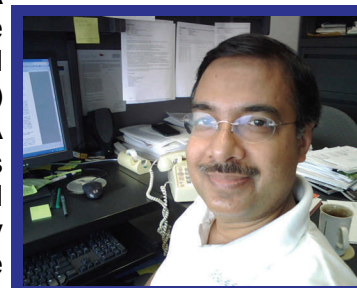


- Debora Botting & Dr. Lillian Chan

Faculty Focus: Tapas K. Hazra, Ph.D.

Associate Professor, Internal Medicine and BMB

Our broad area of research interest is to study repair of oxidative DNA damage in mammalian cells. Oxidatively induced DNA base lesions have been implicated in the etiology of many diseases, including cancer. Oxidized DNA base lesions are primarily repaired via the base excision repair (BER) pathway which is initiated with the excision of the lesion by a specific DNA glycosylase. Human NEIL1 and 2, recently characterized DNA glycosylases primarily by us, are distinct from the other two DNA glycosylases (OGG1 and NTH1) in structural features and reaction mechanism. NEILs preferentially excise oxidized bases from DNA bubble, a transcription or replication bubble mimic. Our preliminary studies indicate that NEILs form a large repair-proficient complex which may primarily be involved in repairing active regions of the genomes. We have also found that downregulation of NEILs induced a mutator phenotype in both human and Chinese hamster lung cell lines. A number of DNA polymorphisms have been found to be associated with the pathophysiology of many common diseases, particularly cancer. We are thus characterizing naturally occurring polymorphic variants of NEILs and screening various cancer tissues. We have found several variants of NEIL genes while analyzing genomic DNA isolated from lung cancer patients. Additionally, we have found differential expression of the DNA glycosylases in pancreatic and lung cancer tissues. These are exciting findings, and we would like to advance our study by understanding the molecular mechanism of differential expression of the DNA glycosylases. We are also characterizing the variants functionally and structurally for a comprehensive understanding of disease pathogenesis. We expect that our study could lead to the development of strategies for improved prevention and treatment of cancer patients via risk-stratification and prognosis.



RESEARCH HIGHLIGHTS

1. The discovery of a new family of mammalian enzymes for repair of oxidatively damaged DNA. (Hazra *et al.* 2002, *PNAS*, 99: 3523-3528; Hazra *et al.* 2002, *J.Biol.Chem*, **277**:30417-30420)
2. Implication of transcription and/or replication coupled repair by new DNA glycosylases. (Dou *et al.* 2003, *J Biol Chem*. 278:49679-49684)
3. Discovery of a new sub-pathway for oxidative damage repair in mammalian genomes. (Wiederhold *et al.*, 2004. *Mol Cell*; 15:209-220; Das *et al.*, 2006. *DNA Repair* 5: 1439-48)
4. Biochemical and cellular characterization of NEIL2 interactome. (Das *et al.* 2007, *J Biol Chem*. 282: 28475-84)

Research in progress

5. Potential etiologic role of NEIL1 and 2 in lung and pancreatic cancer
6. NEIL2-initiated preferential repair of oxidized base damage in the transcribed DNA strands

Administrator's Notes

Debora Botting, Graduate Program Coordinator, has been on medical leave for several weeks and will be returning to work part-time beginning on Monday, June 30. It will be great to have her back.

Dr. Vince Hilser, the Sealy Center for Structural Biology, and the Department of Biochemistry and Molecular Biology welcome **Dr. Linda Roden**, who has been appointed to the position of **Administrator** for the **SCSB**. Linda received an M.D. from Capital Medical University in Beijing, China as well as an MBA from the University of St. Thomas in Houston. Just before coming to UTMB, she was a Project Director in the Clinical and Translational Research Center at M.D. Anderson Cancer Center. Linda also has experience in laboratory research, having been a Research Associate in the Department of Pathology at Baylor College of Medicine.

At the June Faculty Meeting, **Dave Ketchens, Director of Facilities Operations**, discussed the recurring problems with **elevators in MRB and BSB**. Dave outlined the steps that FOAM is taking to improve and monitor elevator performance and to plan for replacement of the most problematic elevators. He said that the elevators in MRB and BSB would be near the top of the priority list for the next replacement effort.

Thanks go to **Lisa Pipper** for working with FOAM to update the **signs outside the Department's labs and offices**. We think we have now changed all the signs to read Biochemistry and Molecular Biology instead of HBC&G.

Steve Stokes, UTMB's Occupational Safety and Fire Prevention Specialist, reported that the **inspection of BMB labs and offices by the State Fire Inspectors** went extremely well; only a small number of minor issues were noted, which were mostly remedied quickly. Steve commended Department members on the effort made to evaluate fire safety compliance and take corrective action in advance of the inspectors' visit - he said we stood out as one of the best-prepared departments. The detailed work undertaken by Lisa Pipper, faculty, administrative staff members, and lab staff yielded excellent results.

- Marianne

FIRSTCALL

*The Department's Safety and Emergency Management Committee **strongly encourages** all BMB members to register a private telephone number or email address in the UTMB **FirstCall** system. Being able to receive broadcast emergency communications from UTMB on a personal phone or email account may be very important if critical events occur outside regular work hours or on a weekend or holiday. The instructions to register can be found [here](#). (To access this link, users must be at a workstation on the UTMB network or connected to the network through VPN.)*

FirstCall augments existing emergency communication resources which send messages through the UTMB email and phone systems. **FirstCall** will be activated only in an emergency situation when there is a serious risk of harm or threat to life. When such a threat occurs, a very brief message will be sent to those registered in the system, instructing them to seek information and updates from other university information sources. The **FirstCall** system is voluntary and optional. To register, faculty, staff and students may use the campus directory to indicate an alternate private email address or telephone number where a broadcast emergency message can be received. This emergency contact information is not displayed in the directory or used for any other purposes.

A **FirstCall** emergency broadcast can be triggered by University Police or UTMB Public Affairs working on behalf of the institutional emergency preparedness officers. The system is supported by Information Services and hosted outside the region by a dedicated service provider.

Hurricane season runs from June 1—November 30. The annual Institution-wide emergency preparedness meeting was held last week and all the material presented can be found online at http://intranet.utmb.edu/emergency_plan/.

Additionally, there will be a special Laboratory Preparedness meeting presented by Environmental Health and Safety on **Thursday, June 26 from 10:30 to 12:00**. BMB Faculty and staff are encouraged to attend this meeting, especially those responsible for chemical and radiation safety.

Department Emergency Planning

The department's Safety and Emergency Management Committee is in the process of updating the emergency plan. The revised plan will be distributed to all faculty and staff as soon as it is completed, and new elements of the plan will be presented at the July Faculty Meeting.

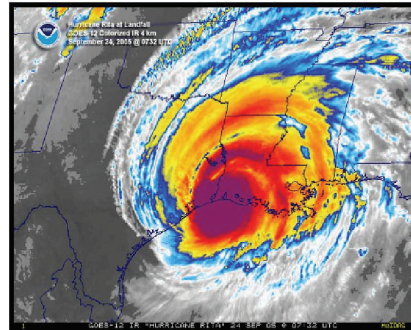
Lisa Pippet will be sending email to all BMB members asking everyone to confirm or update their emergency contact information. Faculty and staff who are new to BMB should be sure to respond as soon as possible. This information is maintained in a Departmental database accessible only to senior Department managers

Personal Hurricane-Preparedness Planning

Now is the ideal time to review personal hurricane plans, both for being able to sustain a household for several days after a Category 1 or 2 storm, and for securing a household and evacuating to an inland location if a more serious storm approaches.

Below are resources to help guide hurricane planning:

- [Your Family Hurricane Plan Checklist](#)
- www.OneStorm.org



Faculty on the Road

Dr. Sankar Mitra visited China on April 13-21 to give a talk at the 2nd International Conference in Biomedical and Environmental Health Sciences: DNA Repair and Cancer Biology, held in Hangzhou, during April 16-20.

Other travel by Dr. Mitra included:

attending the annual Workshop of the NCI Program Project on Structural Cellular Biology of DNA Repair based in Lawrence Berkeley Laboratory, Berkeley, CA on May 8-11.

visiting MD Anderson Science Park on May 20 to give the Annual History of DNA Repair Videoconference lecture which is broadcast to many campuses throughout the country.

traveling to San Juan, Puerto Rico to participate as a member of the Program Advisory Committee for the SNRP of the University of Puerto Rico on May 29-30.



Dr. Wlodek Bujalowski traveled to Washington, D.C., to participate in MSFB Study Section, June 4-7, 2008.

He also attended the Gordon Conference to present paper-"Hexameric Helicases: Protein - Nucleic Acid and Protein-Protein Interactions" at Salve Regina University, Newport, RI, June 8-13th, 2008.

Dr. Satish Srivastava attended and presented at the 2008 Association for Research in Vision and Ophthalmology (ARVO) meeting in Ft. Lauderdale, FL. on April 28th thru April 30th

Dr. Kota V. Ramana traveled to Los Angeles CA April 17th thru April 18th as a reviewer for the American Heart Association Region III Review Study Section.

He also attended and presented at the 2008 Association for Research in Vision and Ophthalmology (ARVO) meeting in Ft. Lauderdale, FL on April 28th thru April 30th.

Dr. Lillian Chan attended the American Society for Gene Therapy Annual Meeting in Boston, MA. May 29th thru June 3rd.

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

Oh, J.H., Young Bun Kim, Y.B., Gurnani, P., **Rosenblatt**, K.P., and Gao, J. (2008) Biomarker selection and sample prediction in multi-stage disease on MALDI-TOF data. *Bioinformatics*, submitted (Co-Senior Author).

Cha, S.-K., Ortega, B., Kurosu, H., **Rosenblatt**, K.P., Kuro-o, M., and Huang, C.-L. (2008) Removal of sialic acid involving Klotho causes cell-surface retention of TRPV5 channel via a binding to galectin-1. *Proceeding of the National Academy of Sciences (USA)*, in press.

Oh, J.H., Young Bun Kim, Y.B., Gurnani, P., **Rosenblatt**, K.P., and Gao, J. (2007) A novel classification method for analyzing multi-stage diseases using MALDI-TOF mass spectra. *Proceedings of the IEEE International Conference on [Bioinformatics and Biomedicine \(IEEE BIBM\) 2007: 237-242](#)* (Co-Senior Author).

Oh, J.H., Kim, Y.B., Gao, J., Nandi, A., Gurnani, P., and **Rosenblatt**, K.P. (2007) Biomarker selection in Alzheimer disease using high-resolution MALDI-TOF data. *Proceedings of the 7th IEEE Symposium on [Bioinformatics and Bioengineering \(IEEE BIBE\) 2007: 464-471, 14-17 October 2007](#)* (Co-Senior Author).

Oezguen, N., Kumar, S., Hindupur, A., **Braun, W.**, Muralidhara, B.K. and Halpert, J.R. Identification and analysis of conserved motifs in cytochrome P450 family 2: Functional and structural role of a Motif 187RFDYKD192in CYP2B enzymes. *J. Biol. Chem.*, May 21. [Epub ahead of print], 2008.

Mark Andrew White, Natalia Mast, Ingemar Bjorkhem, Eric F. Johnson, C. David Stout, and Irina A. Pikuleva, The Use of Complementary Cation and Anion heavy-atom salt derivatives to solve the structure of cytochrome P450 46A1, *Acta Cryst. D* 2008; **65**(16);487-95 **EPUB**: April 20.

Ye Y, Martinez JD, **Perez-Polo JR**, Lin Y, Uretsky BF, **Birnbaum Y**. The role of eNOS, iNOS and NF{ κ }B in upregulation and activation of cyclooxygenase-2 and infarct size reduction by atorvastatin. *Am J Physiol Heart Circ Physiol*. 2008 May 9. [Epub ahead of print]

Handbook of Neurochemistry and Molecular Neurobiology 3rd Edition Development and Aging Changes in the Nervous System; Abel Lajtha (Ed.) Volume Editors **Regino Perez-Polo**, Steffen Rossner Springer, NY 2008.

Joseph, JA & **Perez-Polo JR**. Healthy Aging Strategies In: Handbook of Neurochemistry & Molecular Neurobiology, 3rd Edition Development and Aging Changes in the Nervous System, Ed: J.R. Perez-Polo & S. Rossner, Springer, NY, 2008; Volume 17: 305-317.

Hu, X & **Perez-Polo JR**. Stress Response Signal Transduction In: Handbook of Neurochemistry & Molecular Neurobiology, 3rd Edition Development and Aging Changes in the Nervous System, Ed; J.R. Perez-Polo & S. Rossner, Springer, NY, 2008 Volume 17: 89-102.

Featured Abstract by BMB Faculty

Identification and analysis of conserved motifs in cytochrome P450 family 2: Functional and structural role of a Motif 187RFDYKD192 in CYP2B enzymes.

Oezguen, N., Kumar, S., Hindupur, A., *Braun, W.*, Muralidhara, B.K. and Halpert, J.R. *J. Biol. Chem.*, May 21. [Epub ahead of print], 2008.

Using a multiple alignment of 175 cytochrome P450 family 2 sequences, twenty conserved sequence motifs (CSM) were identified with the program PCPmer. Subsequently, structural analysis of these motifs was performed using ligand-free and 4-(4-chlorophenyl)imidazole (4-CPI)-bound P450 2B4 crystal structures. Functional importance of the CSM in P450 2B enzymes was assessed from available data on site-directed mutants and genetic variants. These analyses suggested an important role of the CSM 8, which corresponds to (187) RFDYKD(192) in P450 2B4. Further analysis showed that residues 187, 188, 190, and 192 have a very high rank order of conservation compared with 189 and 191. Therefore, eight mutants (R187A, R187K, F188A, D189A, Y190A, K191A, D192A, and a negative control K186A) were made in an N-terminal truncated and modified form of P450 2B4 with an internal mutation, which is termed 2B4dH/ H226Y. Function was examined with the substrates 7-methoxy-4-(trifluoromethyl)coumarin (7-MFC), 7-ethoxy-4-(trifluoromethyl)coumarin (7-EFC), 7-benzyloxy-4-(trifluoromethyl)coumarin (7-BFC), and testosterone and with the inhibitors 4-CPI and bifonazole (BIF). Compared with the template and K186A, R187A, R187K, F188A, Y190A, and D192A showed =2-fold altered substrate specificity, $k(\text{cat})$, $K(\text{m})$, and/or $k(\text{cat})/K(\text{m})$ for 7-MFC and 7-EFC, and 3- to 6-fold decreases in differential inhibition ($\text{IC}(50)$, $\text{BIF}/\text{IC}(50)$, 4-CPI). Furthermore, these mutants displayed 5 - 12(0C) decreases in thermal stability ($T(\text{m})$) and 2 - 8(0C) decreases in catalytic tolerance to temperature ($T(50)$) compared with the template and K186A. Furthermore, when R187A and D192A were introduced in CYP2B1dH, the P450 expression and thermal stability were decreased. In addition, R187A showed increased activity with 7-EFC and decreased ($\text{IC}(50)$, $\text{BIF}/\text{IC}(50)$, 4-CPI) compared with 2B1dH. Analysis of long-range residue-residue interactions in the P450 2B4 crystal structures indicated strong hydrogen bonds involving E149-N177-R187-Y190 and D192-V194, which were significantly reduced/abolished by the Arg(187)-Ala and Asp(192)-Ala substitutions, respectively. Similarly, there was a strong pi-pi interaction between Phe-188 and Phe-195, which was abolished by the Phe(188)-Ala substitution.