

BIOCHEMISTRY & MOLECULAR BIOLOGY TODAY

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Chair's Message

A busy March indeed, with adjustments of grant submission deadlines, not to mention new time changes. After months of work and two faculty meetings, a modified faculty compensation plan for tenure track faculty has been submitted to the faculty and approved. Once approved by the Dean of the School of Medicine, this would be put in effect for next year. Also, we will make sure to review the document on a regular basis to make sure that it remains a useful instrument. We now have a committee that is addressing the role of the non-tenure track faculty. More to come on this issue.

UTMB has received \$30 million in PUF funds for a research building and has requested \$60 million more. Given that a new president is coming on board, we are told it is very likely we will receive the additional funds. This will enable construction of a research building of about 150,000 square feet.

It has been proposed that in the future, access to Clay Hall will require a properly activated UTMB ID, as is the case now for Basic Sciences and the Blocker MRB. This is being done at the request of our colleagues working there. We will announce the change in access as soon as it is implemented.

If any of our faculty are planning to submit a grant for a June deadline and you wish to make a "pre-submission" to our in-house Study Section, please let David Konkell or myself know as soon as possible. It will take some planning to assemble the reviewers and block time on their calendars for this function. The draft version will receive the equivalent of a Study Section review by faculty who have Study Section experience. If you are not sure if this would be of help to you, feel free to contact me and we will discuss it.

for his well-deserved promotion to Associate Professor of Biochemistry and Molecular Biology.

Also, congratulations are in order to our assistant professor, Dr. Olivera Nestic. She has been awarded the 2007 Erica Nader Award by the American Spinal Injury Association (ASIA), ASIA's most prestigious award sponsored by Viscogliosi Brothers, for her outstanding work in the area of proteins that contribute to edema and syringomyelia after spinal cord injury. The award will be presented at the annual ASIA meeting in Tampa in June. Well done, Olivera!

Enjoy the spring weather!

regino

Congratulations to Dr. Tapas Hazra

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Special Items of Interest

- New - Faculty Focus, Kay Choi, Ph.D., [page 3](#)
- Research Spotlight, Heidi Spratt, Ph.D., Bioinformatics— [page 4](#)
- [Dr. Konkell's Research Coordinator's Columns Online](#) (new columns to resume in April)

IN MEMORIAM

Diane M. Strain

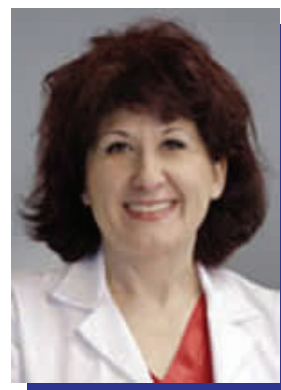


The Department sends its sympathy to the family of Diane M. Strain, who passed away on March 21 from complications of a major injury she sustained in December. Diane came to BMB in January 2001 and quickly became a key member of the Department's administrative staff team. Mostly recently, she was assisting Dr. John Papaconstantinou and Dr. Darrell Carney and supporting Dr. Papa's program project. She was a master at the big things - such as organizing new administrative processes – as well as very small details like interpreting the fine print on the Animal Handling Protocol forms. Many of us relied on her for advice about preparing grant proposals and reports, and we looked for her input on every major research support issue. No matter what came up, she was a complete professional, who "got" the Department's mission, actively looked for ways she could contribute, and maintained her wry sense of humor throughout. Her absence will be felt in many areas, for a very long time.

Marianne Miller

Awards and Announcements

Dr. Olivera Nestic was chosen as UTMB Research Services Researcher of the Month for March: to read more information, please visit the Research Services site at <http://research.utmb.edu/RoM/NesticO0703.pdf>



Dr. Umesh Yadav, a post-doc in Dr. Satish Srivastava's lab has been selected out of 1,500 applicants to receive the ARVO Foundation for Eye Research/Retina Research Foundation/ Joseph M. and Eula C. Lawrence Travel Scholarship Travel Grant to attend and present his abstract at the upcoming ARVO Annual Meeting, May 6-10, 2007 in Fort Lauderdale, Florida.

Faculty Focus: Kay Choi, Ph.D., Assistant Professor, BMB

Dr. Kyung (Kay) Choi received her Ph.D. from the department of chemistry at Boston University in 1998. As a graduate student, she determined the crystal structure and specificity of ginger proteases. She then took a post-doctoral research position in the laboratory of Karen Allen at Boston University School of Medicine, where she also worked with Dean Tolan at Boston University. Her research involved structural and mechanistic enzymology of fructose-1,6-bisphosphate aldolases using a combination of X-ray crystallography and enzyme kinetics. In 2002, she joined the laboratory of Dr. Michael Rossmann at Purdue University as a research assistant scientist. Her research at Purdue focused on structural studies of Flaviviridae replicases and bacteriophages using X-ray crystallography, cryo-electron microscopy, and high-throughput techniques. Dr. Choi joined the faculty of BMB in February 2007.



Our research focuses on the structure and mechanism of viral replication and infection machinery using X-ray crystallography and cryo-electron microscopy. Atomic resolution structures of large complexes (up to several thousand Å in diameter) can be obtained by the combination of these two techniques.

Virtually all RNA viruses carry out viral genome replication using a large replication complex composed of RNA, viral replicases (i.e., polymerase, helicase, protease), and cellular proteins. However, specific protein-protein and protein-RNA interactions are still poorly understood. We are interested in the structure of individual replication enzymes and their protein-protein, and protein-RNA complexes in human and animal viruses. These viruses include hepatitis C virus, bovine viral diarrhea virus (BVDV), dengue virus, human coronavirus (SARS), and hantavirus. Our structural studies will help develop antiviral therapeutics for animal and human diseases caused by these RNA viruses.

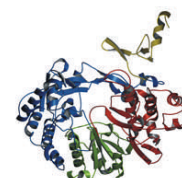


Figure 1: Crystal structure of BVDV polymerase. The N-terminal, fingers, palm, and the thumb domains are shown in yellow, blue, green, and red, respectively.

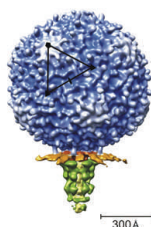


Figure 2: Structure of bacteriophage N4 determined by cryo-EM and 3D image reconstruction techniques.

Tailed bacteriophages have to deliver their genetic information into the host cell's cytoplasm across cell membranes. The tail machinery, composed of multiple protein components, attaches to the cell membrane and transports genomic DNA into the cell. We use bacteriophage N4 as a model system to study the mechanism of genome and protein transport from the virus into the host cell. N4 packages dsDNA as well as one or two copies of a 3,500-amino acid RNA polymerase inside the capsid, which is then ejected into host cell upon infection. In collaboration with Dr. Lucia Rothman-Denes laboratory (University of Chicago), we are determining the structure of N4 virions, including their tail component proteins.

Selected publications

- Choi KH, Gallei A, Becher P, Rossmann MG. (2006) The structure of bovine viral diarrhea virus RNA-dependent RNA polymerase and its amino-terminal domain. *Structure* 14(7):1107-13.
- Choi KH, Lai V, Foster CE, Morris AJ, Tolan DR, Allen KN (2006) New superfamily members identified for Schiff-base enzymes based on verification of catalytically essential residues. *Biochemistry* 18;45(28):8546-55.
- Choi KH, Morais MC, Anderson DL, Rossmann MG. (2006) Determinants of bacteriophage phi29 head morphology. *Structure* 14(11):1723-7.
- Morais MC, Choi KH, Koti JS, Chipman PR, Anderson DL and Rossmann MG. (2005) Conservation of the capsid structure in tailed dsDNA bacteriophages: the pseudoatomic structure of phi29. *Mol Cell*. 18(2):149-59. (Cover illustration of *Molecular Cell*)
- Choi KH, Groarke JM, Young DC, Kuhn RJ, Smith JL, Pevear DC, Rossmann MG. (2004) The structure of the RNA-dependent RNA polymerase from bovine viral diarrhea virus establishes the role of GTP in de novo initiation. *Proc Natl Acad Sci U S A*. 101(13):4425-30.
- Choi KH, Tolan DR. (2004) Presteady-state kinetic evidence for a ring-opening activity in fructose-1,6-(bis)phosphate aldolase. *J Am Chem Soc*. 126(11):3402-3.
- Choi KH, Groarke JM, Young DC, Pevear DC, Rossmann MG, Kuhn RJ, Smith JL (2004) Design, expression, and purification of a Flaviviridae polymerase using a high-throughput approach to facilitate crystal structure determination. *Protein Science* 13 (10):2685-2692
- Pezza JA, Choi KH, Berardini TZ, Beermink PT, Allen KN, Tolan DR. (2003) Spatial clustering of isozyme-specific residues reveals unlikely determinants of isozyme specificity in fructose-1,6-bisphosphate aldolase. *J. Biol. Chem*. 278(19):17307-13.
- Choi KH, Shi J, Hopkins CE, Tolan DR, Allen KN. (2001) Snapshots of catalysis: the structure of fructose-1,6-(bis)phosphate aldolase covalently bound to the substrate dihydroxyacetone phosphate. *Biochemistry*. 40(46):13868-75.
- Choi KH, Laursen RA. (2000) Amino-acid sequence and glycan structures of cysteine proteases with proline specificity from ginger rhizome *Zingiber officinale*. *Eur. J. Biochem*. 267(5):1516-26.
- Choi KH, Mazurkie AS, Morris AJ, Utheza D, Tolan DR, Allen KN. (1999) Structure of a fructose-1,6-bis-(phosphate) aldolase liganded to its natural substrate in a cleavage-defective mutant at 2.3 Å. *Biochemistry*. 38(39):12655-64.
- Choi KH, Laursen RA, Allen KN. (1999) The 2.1 Å structure of a cysteine protease with proline specificity from ginger rhizome, *Zingiber officinale*. *Biochemistry*. 38

Spotlight: Heidi Spratt, Ph.D., Bioinformatics Program

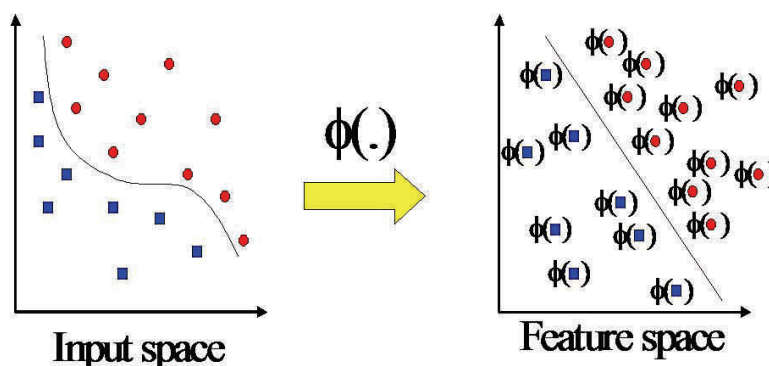
My research area of interest is in Bioinformatics with special considerations given to the mathematical discovery of biomarkers. Using the tools of mathematical modeling and machine learning, I am able to create classifiers to accurately predict disease outcome, discover the best treatment options for disease, examine disease prognosis, or learn more about drug discovery. The methods of machine learning allow for multiple types of input, which make it extremely well-suited for use in a clinical/translational setting. I have



been working with support vector machines (SVMs) which operate by finding a separating hypersurface (think: a line in multidimensional space) to accurately distinguish one group from another. The theory behind machine learning algorithms is that by utilizing both a training set and a testing set of data, one can check the accuracy of the classifier or model to build the best possible set of biomarkers. Once the classifier has been created, researchers can use it to predict the outcome or best treatment options for future patients. SVMs operate by utilizing a kernel function to discriminate between groups of data. The beauty of this kernel function is that it provides a stable platform so that the model will always converge and it also projects the data onto higher dimensional space so that you will always be able to find linearly separable groups. Some important features of support vector machines are that they are data independent – they work for multiple types of data sources as well as combinations of data at once. They also use a linear separation to solve nonlinear problems.

I am also actively involved in developing methods to combine various types of data as well as optimizing the kernel functions which are at the heart of the machine learning algorithms. I initiated a biomarkers workgroup which meets once a week to discuss applications and algorithms for investigation. Machine learning algorithms, and specifically SVMs, have been shown to work well for protein-protein interaction prediction, gene functional classification from microarray data, cancer classification from omics data, splice site recognition, protein sequence similarity detection, protein functional classification, and regulatory module searches among others. If anyone is interested in attending the biomarkers workgroup, or has a project that you think would benefit from these methods, please feel free to contact me hespratt@utmb.edu, x 28100.

Support Vector Machine



Administrator's Notes

Time-and-Effort Reporting

On March 26, the Office of Sponsored Projects (OSP) sent out to all research-supported staff and faculty, instructions for completing online effort reports for the period of September 2006 through February 2007. (The specific periods are slightly different for weekly and bi-weekly faculty and staff.) Although OSP stipulates that the reports should be completed within 30 days, **we are asking BMB personnel to complete the reports on or before Monday, April 13.** Because there have been certain difficulties with implementation of the new salary/payroll system, we will be sampling some of the time-and-effort reports to confirm that the salary information presented in the system is correct. If any inconsistencies are noted, we will review the report with the individual faculty or staff member to determine whether any corrections might be needed. Thanks to everyone involved for your anticipated cooperation on this critically important task.

Temporary Administrative Staff

To help us keep the administrative machinery going while we are short of regular staff, we have recruited two and a half temporary secretaries. Sher Owen is working full-time at Diane Strain's desk assisting Dr. Papaconstantinou and Dr. Carney and performing work in Peoplesoft, especially with placing certain orders. Aurora Ruiz is using the desk just inside 107 Basic Science Building. She is working full-time providing essential administrative services for Dr. Braun, Dr. Schein, and soon Dr. Gorenstein, as well as assisting me in covering the more complex tasks of managing grants for those faculty members. Ana Lyons is working part-time on special administrative projects relating to faculty recruitment, preparation of records for archiving, and data entry for major reports. All three secretaries have learned about the Department very quickly and began right away to shoulder as much of the workload as they could. We appreciate the assistance that Department members have provided in helping them become oriented to BMB operations.

Important Accomplishment by Steve Hathorn

Steve Hathorn has been instrumental in preparing the lab suite on the second floor of BSB, formerly assigned to the Molecular Biology Training Lab, for conversion to other uses. Steve has organized and managed distribution of the equipment and supplies; taken care of disposing of chemicals and other remaining items appropriately; and coordinated work by FOAM to prepare the space for the transition in use. This is an example of the out-of-the-ordinary tasks that seem to come up with some frequency in a complex department such as this one, and we know we can count on Steve to handle these types of things with efficiency and appropriate attention to detail. Thank you for all your efforts on this, Steve.

-Marianne

Featured Abstract by BMB Faculty

Molecular Dissection of $\phi 29$ Scaffolding Protein Function in an *in Vitro* Assembly System

Chi-yu Fu¹, Marc C. Morais², Anthony J. Battisti², Michael G. Rossmann² and Peter E. Prevelige, Jr.³ ¹Department of Biochemistry and Molecular Genetics, University of Alabama at Birmingham, AL35294, USA ²Department of Biological Sciences, Purdue University, 915 West State Street, West Lafayette, IN 47907, USA ³Department of Microbiology, University of Alabama at Birmingham, AL 35294, USA

[Full Text Link](#)

An *in vitro* assembly system was developed to study prolate capsid assembly of phage $\phi 29$ biochemically, and to identify regions of scaffolding protein required for its functions. The crowding agent polyethylene glycol can induce bacteriophage $\phi 29$ monomeric capsid protein and dimeric scaffolding protein to co-assemble to form particles which have the same geometry as either prolate $T = 3 Q = 5$ procapsids formed *in vivo* or previously observed isometric particles. The formation of particles is a scaffolding-dependent reaction. The balance between the fidelity and efficiency of assembly is controlled by the concentration of crowding agent and temperature. The assembly process is salt sensitive, suggesting that the interactions between the scaffolding and coat proteins are electrostatic.

Three N-terminal $\phi 29$ scaffolding protein deletion mutants, $\Delta 1-9$, $\Delta 1-15$ and $\Delta 1-22$, abolish the assembly activity. Circular dichroism spectra indicate that these N-terminal deletions are accompanied by a loss of helicity. The inability of these proteins to dimerize suggests that the N-terminal region of the scaffolding protein contributes to the dimer interface and maintains the structural integrity of the dimeric protein.

Two C-terminal scaffolding protein deletion mutants, $\Delta 79-97$ and $\Delta 62-97$, also fail to promote assembly. However, the secondary structure and the dimerization ability of these mutants are unchanged relative to wild-type, which suggests that the C terminus is the likely site of interaction with the capsid protein.

Faculty on the Road

Dr. Awasthi attended the Asia ARVO meeting on Research in Vision and Ophthalmology in Singapore on, March 2-5, 2007 where he presented a poster on "Regulation of the Expression and Functions of Fas (DC95) by 4-Hydroxynonenal in Human Lens Epithelia (HLE B-3) Cells."

Dr. Catherine Schein presented a poster on her design of inhibitors of Anthrax at the ASM Biodefense meeting Feb 27-March 2.

Dr. Sankar Mitra was an invited speaker at the Gordon Conference on Mammalian DNA Repair in Ventura, CA on February 4-9.

Dr. Mitra was also an invited speaker at the Golden Jubilee Symposium of the Indian Institute of Chemical Biology (IICB), in Kolkata, March 7-9, 2007.

Dr. Cheryl Watson traveled to Washington D.C. March 9-11, 2007 to attend the membership committee meeting for the Endocrine Society.



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.

New Employees

Jenny Gu, Ph.D., Postdoctoral Fellow with Dr. Hilser's lab.

Muniasamy Neerathilingam, Ph.D., Postdoctoral Fellow
with Dr. Luxon's lab.

Elena Sineva, Ph.D., Postdoctoral Fellow with Dr. L. Prakash's lab.

Leslie Streeter, Ph.D., Postdoctoral Fellow with Dr. Gorenstein's lab.

Publications

Jörg Rösgen, B. Montgomery Pettitt, and **David Wayne Bolen** (2007) An analysis of the molecular origin of osmolyte-dependent protein stability. *Protein Science* 16:733-743.

Fu CY, **Morais MC**, Battisti AJ, Rossmann MG, Prevelige PE J. Molecular Dissection of phi29 scaffolding protein in an in vitro assembly system. *J Mol Biol* 2007 Mar 2;366 (4):1161-73.

Deliang Chen, Gerd Menche, Trevor D. Power, Laurie Sower, Johnny W. Peterson, **Catherine H. Schein** Accounting for ligand-bound metal ions in docking small molecules on adenyl cyclase toxins. *Proteins*. 2007 Feb 20; [Epub ahead of print].

Iwahara, J., Jung, Y.S., Clore, G.M. (2007) Heteronuclear NMR spectroscopy for lysine NH3 in proteins: Unique effect of water-exchange on 15N transverse relaxation. *J. Am. Chem. Soc.* 129, 2971-2980.

Suh, J.Y., **Iwahara, J.**, Clore, G.M. (2007) Intramolecular domain-domain association/dissociation and phosphoryl transfer in the mannitol transporter of *Escherichia coli* are not coupled. *Proc. Natl. Acad. Sci. U. S. A.* 104, 3153-3158.

Iwahara, J., Tang, C., Clore, G.M. (2007) Practical aspects of 1H transverse paramagnetic relaxation enhancement measurements on macromolecules. *J. Magn. Reson.* 184, 185-193.

Mitra, S., Izumi, T., Boldogh, I., **Bhakat, K. K.**, Chattopadhyay, R. and Szczesny, B. Intracellular Trafficking and Regulation of Mammalian AP-endonuclease 1 (APE1), An Essential DNA Repair Protein. *DNA Repair* Special Issue. 6:461-469, 2007.

Atasheva S, Gorchakov R, English R, Frolov I, **Frolova E**. Development of Sindbis viruses encoding nsP2/GFP chimeric protein and their application for studying nsP2 functioning. *J Virol.* 2007 Feb 28; [Epub ahead of print]

Garmashova N, Gorchakov R, Volkova E, Paessler S, **Frolova E**, Frolov I. The Old World and New World alphaviruses use different virus-specific proteins for induction of transcriptional shutoff. *J Virol.* 2007 Mar;81(5):2472-84. Epub 2006 Nov 15.

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