Nucleus

OFFICE OF THE ASSOCIATE DEAN FOR RESEARCH

Texas Tech University Health Sciences Center
School of Pharmacy

http://www.ttuhsc.edu/sop/research/

VOLUME 2, ISSUE 2

SPECIAL POINTS OF INTEREST:

- **Marsh Lecture**
- **Research Days '06**
- **ABRI Program**
- **Dissertation Defenses**
- **Dr. Abbruscato study section member**

INSIDE THIS ISSUE:

Dr. Smith Receives NIH Grant

Quentin Smith, Ph.D. recently received an NIH grant to study modeling drug uptake into brain and the role of plasma protein binding. The grant will be funded for four years.

Drug delivery to brain is limited by the blood-brain barrier (BBB) (i.e., neurovascular unit) which markedly impacts treatment for many central nervous system (CNS) diseases. Of the various BBB factors that limit brain drug delivery, one of the least well understood is the contribution of plasma protein binding, which involves a complex interplay between brain blood flow, the brain capillary glycocalyx and plasma membrane, and the free and bound drug concentrations in the capillary circulation. Most drugs bind significantly to plasma proteins: approximately half bind 90% or more. For some, plasma protein binding dramatically reduces brain uptake and distribution, whereas for others, there is little or no effect. The great majority of BBB drug transport studies report greater brain uptake than can be accounted for based upon the free fraction of drug in plasma and have suggested that special interactions occur in the capillary circulation leading to "enhanced dissociation" *in vivo*. The net effect is that this has impeded understanding and prediction of CNS drug penetration in drug development and clinical analysis. The primary hypothesis of this grant is that brain uptake for many drugs can be predicted using a modified Crone-Renkin model that incorporates drug dissociation and rebinding to plasma proteins in the brain capillary in addition to free drug uptake and exchange with brain. This hypothesis will be pursued through four specific aims: (1) to confirm using a carefully controlled *in situ* rat brain perfusion technique that initial, unidirectional drug uptake into brain can be predicted for many drugs with a simple model based upon four readily determined parameters - the arterial input drug concentration, the free fraction (fu) of drug in the arterial input, the apparent BBB permeability-surface area product (PSu) to free (unbound) drug, and the flow rate of fluid through the brain vasculature (F); (2) to evaluate the rates of drug dissociation and rebinding to plasma protein and their influence on initial drug uptake into brain for drugs that exhibit high capillary extraction at defined flow rate; (3) to show using the perfusion technique that plasma protein binding directly affects the steady state distribution of drug in brain; and (4) to validate using the Nagase albumin knockout rat that this same relationship holds *in vivo* and that brain drug concentration at steady state is driven ultimately by the plasma free drug concentration and the brain drug distribution volume. This research will provide a novel mechanism to distinguish drugs that exhibit restrictive vs. nonrestrictive plasma protein binding effects on brain uptake, will provide a rational means upon which to base CNS drug-dosing for agents that bind significantly to plasma proteins, and will assist in selection of agents with optimal brain delivery in CNS drug development. The critical importance of this work to public health is that it will improve our ability to readily predict and identify new drug agents that cross the BBB for the treatment of CNS diseases.

Congratulations, Dr. Smith!

9th Annual Marsh Endowed Lectureship

R. Adron Harris, Ph.D., presented this year's Wendy & Stanley Marsh 3 Endowed Lectureship in Pharmacology and Neurochemistry of Substance Abuse/ Addiction. Dr. Harris is the Director of the Waggoner Center for Alcohol and Addiction Research, holds the M. June and J. Virgil Chair in Molecular Biology, and is a professor of Neurobiology at the University of Texas at Austin.

Dr. Harris presented "Sites of Alcohol and Anesthetic Action: From Molecules to Mice" for the lecture on March 21. The Grand Rounds on March 22 was co-sponsored by the School of Medicine's Department of Continuing Education (CME credits were offered to attendees). For the Grand Rounds presentation, Dr. Harris lectured on "Molecular Medicine Meets Addiction Treatment."

A reception followed the lecture, and lunch was provided at the Grand Rounds for all attendees.

TTUHSC faculty members, pharmacy and graduate students, pharmacy residents, instructors and professors from other area colleges/universities, area clinicians and mental health professionals enjoyed Dr. Harris' presentations. Several attendees offered comments about Dr. Harris' lectures, describing him as "an engaging, interesting speaker," "an entertaining lecturer," and "a personable guy." After the lecture, a couple of faculty members were excitedly talking about the pertinence of Dr. Harris' presentation: "This was *exactly* what I just tried to teach my students!"

In addition to his lectures, several School of Pharmacy faculty members also enjoyed individual office visits with Dr. Harris and universally described him as friendly and impressive. For TTUHSC faculty members, being able to discuss research ideas and projects with scientists of Dr. Harris' caliber is a significant benefit of the Marsh Endowed Lectureship. At least one excited faculty member made plans to visit Dr. Harris at the University of Texas. Our thanks go out to Dr. Harris for being such an excellent speaker and personable guest. We also would like to thank Wendy and Stanley Marsh 3 for their continuing support of this event.

We look forward to future years of these Marsh Endowed Lectureships, which bring internationally-recognized experts in the field of pharmacology and neurochemistry to our area.

A Different Research Days Event

Research Days has been scheduled this year for Wednesday, August 2 through Friday, August 4.

Those who have attended previous years' events may note that the event has been extended by a day. This will accommodate a special all-day grant-writing seminar provided by Grant Writers' Seminars & Workshops, LLC.

Research Days will begin as usual, around noon on Wednesday, August 2. Thursday will be a break from Research Days, and faculty members are invited to attend the grant-writing seminar; however, RSVPs will be needed by the Office prior to the seminar. Additional information will be sent out as we get closer to the date. Then, regular Research Days activities will resume and conclude on Friday, August 4.

This year, the ad hoc Research Advisory Committee decided to identify a theme for Research Days activities. They are still in the process of perfecting that theme and identifying a speaker. Announcements will be coming soon, but in the meantime, please mark your calendars for the 5th Annual Research Days: August 2 & August 4. And again, for faculty, the grant-writing seminar will be on August 3.

Hope to see you all at Research Days!

Enhancement Grants

After approving a request from the Office of Research for special funding support, President Wilson and Dr. Nairn made possible the awarding of Enhancement Grants for 2006. These grants are intended to provide special funding support for investigators seeking to pursue their extramurally-fundable, novel ideas. These grants are only for FY06 but will hopefully provide the necessary funding for awardees to secure extramural funding that will sustain their work.

Applications for the FY06 Enhancement Grants have been received by the Office of Research and have been evaluated by senior faculty reviewers. The ad hoc Research Advisory Committee has also met to give their input and make the final recommendations.

The final decisions and award announcements will be coming soon. Please watch for additional information.

ABRI Program for Summer 2006

The official start date for the ABRI summer research internship program has been set for Monday, May 29, 2006. We have been receiving applications from interested students, even from other states. The participating faculty mentors and Office of Research will be making final selections from among these candidates very soon.

Just like last year, selected interns will be placed in research laboratories, under faculty mentors who have ongoing, already-established, investigator-initiated research projects. Interns will work for 10 weeks and will present their results and accomplishments through poster presentations at Research Days (August 2 & 4). Please be on the lookout for these visiting researchers over the summer months and welcome them to the School of Pharmacy.

For additional information about the ABRI program, please visit: http://www.ttuhsc.edu/sop/research/abri.aspx

PhD Candidates Defend Their Dissertations

Nusrat Motlekar, PhDc defended her dissertation entitled "Absorption enhancer based formulation for the oral delivery of low molecular weight heparin" on February 24, 2006.

Nusrat arrived at the School of Pharmacy in the fall of 2001 and began her MS work under the guidance of Dr. Bibotti Celestin Youan. She obtained her MS Fall 2003 and continued toward pursuit of a PhD in the same lab.

She has recently authored several manuscripts based on her dissertation research, including articles published in the following journals: *Journal of Controlled Release, Journal of Pharmacy and Pharmacology, Journal of Drug Development Research* and the *Journal of Drug Targeting.* She has published two articles based on her MS research in Pharmaceutical Sciences in the *Journal of Applied Polymer Science* and *Pharmaceutical Technology.*

Over the course of her studies, Nusrat examined the effects of various absorption enhancers, namely, sodium caprate, glycyrrhetinic acid, Zonula occludens toxin fragment AT1002, and l-arginine on altering the permeation of low molecular weight heparin in cell-culture model and rat. This effect can potentially have clinical benefit for patients undergoing therapy for deep vein thrombosis and pulmonary embolism.

Nusrat credits much of her success while here to the support of her colleagues and her mentor, Dr. Celestin Youan. At present, she is working on submitting additional papers related to her dissertation research. She is actively looking for a suitable position in research and development with a focus on drug delivery formulations.

Vaughan Wittman, PhDc defended "A Full-Length, Peptide-Specific, HLA-Restricted TCR Mimic Antibody Promotes Tumor Cell Death" on March 29, 2006. Vaughan worked with Dr. Weidanz to study the effects of the renin-angiotensin system on T cells. Before coming to TTUHSC, his previous work experience included working as a clinical microbiologist and over 20 years in the biotechnology sector as a research associate, associate scientist and senior scientist. His experience in industry focused on the molecular characterization, expression, and manipulation of receptors of the immune system. Vaughan's primary field of research while here at TTUHSC was aimed at understanding the signaling pathways generated via the angiotensin receptors and the impact this signaling has on cellular response at the different stages of T cell development. A secondary interest was the delivery to and expression of recombinant receptor molecules on human T cells.

PhD Candidates Defend Their Dissertations (continued from page 3)

Young Tag Ko, PhDc defended his dissertation, entitled "Nanoparticle-Based Delivery of Gene Therapeutics to the Blood-Brain Barrier" on March 24, 2006. Before coming to TTUHSC, Ko earned his BS (Pharmacy) and MS (Pharmacy, specializing in chemical analysis) from the Seoul National University (Seoul, Korea). After working at a pharmaceutical company for six years (Jassen Korea Ltd, Seoul, Korea) and chemical analysis company for one year (Agilent Technologies Korea Ltd, Seoul, Korea,) he came to TTUHSC to earn a PhD in Pharmaceutical Sciences. Working in Dr. Bickel's lab, his research interests included polymer-based gene delivery systems. Efficient delivery is a major barrier to gene therapy. Ko's research focused on the development of a new gene delivery system for *in vivo* application. This included a new liposomal formulation encapsulating polymer/DNA complex.

Research Seminars

During the school year, faculty and graduate students present research seminars highlighting their work. Below is a summary of the seminars that took place in the last few months.

2/20/06-Julie Gaasch, Graduate Student, Department of Pharmaceutical Sciences. "Iron toxicity in neuronal cell cultures is mediated in part by iron uptake via L-type calcium channels."

2/24/06-Nusrat Motlekar, Ph.D.c, Department of Pharmaceutical Sciences. Dissertation Defense. "Absorption Enhancer Based Formulation for the Oral Delivery of Low Molecular Weight Heparin."

3/6/06-Jiukuan Hao, Graduate Student, Department of Pharmaceutical Sciences. "Receptor-Mediated Brain Uptake and Blood Flow in a Stroke Model."

3/13/06-Shuhua Bai, Graduate Student, Department of Pharmaceutical Sciences. "Long Circulating Formulations of LMWH for Pulmonary Delivery."

3/24/06-Young Tag Ko, PhDc, Department of Pharmaceutical Sciences. Dissertation Defense. "Nanoparticle-Based Delivery of Gene Therapeutics to the Blood-Brain Barrier."

3/29/06-Vaughan Wittman, PhDc, Department of Pharmaceutical Sciences. Dissertation Defense. "A Full-Length, Peptide-Specific, HLA-Restricted TCR Mimic Antibody Promotes Tumor Cell Death."

Invited Talks

Akins R & Haase M. "Antibiotics Across the Lifespan: Appropriate Utilization in an age of Microbial Resistance." TTUHSC School of Nursing Continuing Nursing Education Program, 10th Annual Nurse Practitioner Workshop. March 3, 2006.

Abbruscato TJ. "Brain Aspects of Ischemia and Nicotine." Department of Neuroscience and Experimental Therapeutics, Texas A&M College of Medicine, College Station, Texas. January 23rd, 2006.

Smith Quentin R. "How Well Do Standard Chemotherapeutics Enter Brain and Brain Tumors." Twelfth Annual Neuron-Oncology and Blood-Brain Barrier Disruption Meeting, Sunriver, Oregon. March 23-25, 2006

Publications (January-March 2006)

Bazinet RP, **Weis MT,** Rapoport SI, Rosenberger TA. Valproic acid selectively inhibits conversion of arachidonic acid to arachidonoyl-CoA by brain microsomal long-chain fatty acyl-CoA synthetases: relevance to bipolar disorder. *Psychopharmacology (Berl).* 2006 Jan;184(1):122-9. Epub 2005 Dec 13.

Bond CA, **Raehl CL.** Adverse drug reactions in United States hospitals, *Pharmacotherapy*, in press, 2006;25(5).

Publications (continued from page 4)

Chimalakonda AP, Montgomery DL, **Weidanz JA**, **Shaik IH**, Nguyen JH, Lemasters JJ, Kobayashi E, **Mehvar R**. Attenuation of acute rejection in a rat liver transplantation model by a liver-targeted dextran prodrug of methylprednisolone. *Transplantation*. 2006 Mar 15;81(5):678-85.

Crews F.T., **Mdzinarishvili A.,** Kim D., He J., Nixon K. Neurogenesis in Adolescent Brain is Potently Inhibited by Ethanol. *Neuroscience* 137 (2006) 437–445.

Geldenhuys WJ, Gaasch KE, Watson M, Allen DD, **Van der Schyf CJ.** Optimizing the use of open-source software applications in drug discovery. *Drug Discov Today*. 2006 Feb;11(3-4):127-32.

Grobler E, Grobler A, **Van der Schyf CJ**, Malan SF. Effect of polycyclic cage amines on the transmembrane potential of neuronal cells. *Bioorg Med Chem.* 2006 Feb 15;14 (4):1176-81. Epub 2005 Oct 24.

Haase M. Cerebral Palsy, book chapter in *Pharmacotherapy Self Assessment Program*, 5th edition, book 9. Jan 2006.

Irons BK, Greene RS, Mazzolini TA, Edwards KL, Sleeper RB. Implications of rosiglitazone and pioglitazone on cardiovascular risk in patients with type 2 diabetes mellitus. *Pharmacotherapy*. 2006 Feb;26 (2):168-81.

Motlekar Nusrat A., Fasano Alessio, Wachtel Mitchell S., **Youan Bi-Botti C.** (2006) Zonula Occludens Toxin enhances oral bioavailability of low-molecular-weight-heparin. *Journal of Drug Targeting* (in press).

Motlekar Nusrat, Khan Mansoor A., Nguyen Nga. T., Youan BBC (2006) Enhanced Genistein Dissolution Profile Following Microencapsulation Into Poly (ethylene glycol) Matrix. *Journal of Applied Polymer Science* (in press).

Motlekar Nusrat A., Srivenugopal Kalkunte S., Wachtel Mitchell S., **Youan, BBC** (2006) Evaluation of the oral bioavailability of low molecular weight heparin formulated with glycyrrhetinic acid as permeation enhancer. *Drug Development Research* (in press).

Motlekar Nusrat A., Srivenugopal Kalkunte S., Wachtel Mitchell S., **Youan BBC** (2006) Modulation of gastrointestinal permeability of low molecular weight heparin by L-arginine: *In vivo* and *in vitro* evaluation. *Journal of Pharmacy and Pharmacology* (in press).

Motlekar Nusrat A., Srivenugopal Kalkunte S., Wachtel Mitchell S., **Youan BBC** (2005; not included in previous *Nucleus* issues) Oral delivery of low-molecular-weight heparin using sodium caprate as absorption enhancer reaches therapeutic levels. *Journal of Drug Targeting* 13(10): 573-83.

Motlekar Nusrat A., Youan Bi-Botti C. (2006) The Quest for Noninvasive Delivery of Bioactive Macromolecules: A Focus on Heparins. *Journal of Controlled Release* (in press).

Muldoon LL, Tratnyek P, Jacobs PM, Doolittle ND, Christoforidis GA, Frank J, Lindau M, **Lockman PR**, Manninger S, Qiang Y, Spence A, Stupp S, Zhang M, Neuwelt E. (2006) Imaging and nanomedicine for diagnosis and therapy in the CNS: Report of the eleventh annual blood-brain barrier disruption consortium meeting. *Am J Neuroradiol* 27(3) 715-21.

Paulson J.R., Roder K.E., McAfee G., Allen D.D., Van der Schyf C.J., Abbruscato T.J. Tobacco smoke chemicals attenuate brain-to-blood potassium transport mediated by Na,K,2Cl-cotransporter during hypoxia-reoxygenation. *J. Pharmacol. Exp. Ther.* 316 (1): 248-254, 2006.

Samikkannu T, Thomas JJ, Bhat GJ, Wittman V, Thekkumkara TJ. Acute Effect of High Glucose on Long-term Cell growth: A Role for Transient Glucose Increase in Proximal Tubule Cell Injury. *Am J Physiol Renal Physiol* 2006 Feb 7; [Epub ahead of print]

Tsikouris JP, **Peeters MJ, Cox CD**, Meyerrose GE, **Seifert CF**. Effects of three fluoroquinolones on QT analysis after standard treatment courses. *Ann Noninvasive Electrocardiol.* 2006 Jan;11(1):52-6.

Yang T., Roder K.E., Bhat G.J., Thekkumkara T.J., Abbruscato T.J. Protein kinase C family members in the regulation of blood-brain barrier Na,K,2Cl-cotransporter during in vitro stroke conditions and nicotine exposure. *Pharm. Res.* 23(2): 291-302, 2006.

Youan BBC (2006). Influence of protein content on the physico-chemistry of poly (epsilon caprolactone) microparticles. *Journal of Applied Polymer Science* (in press).

Name in the News

Thomas Abbruscato, PhD has been formally appointed to an NIH study section as a regular member. He will be serving a four-year regular membership on the Brain Injury Neurovascular Pathologies (BINP) NIH Study Section for the National Institute of Neurological Disorders and Stroke. Please congratulate Dr. Abbruscato!

Tenures Awarded and Academic Ranks Changed

At the February meeting of the Board of Regents, Roderick Nairn, Ph.D., Executive Vice-President for Academic Affairs, presented several Health Sciences Center faculty members to be considered for tenure or changes in academic rank.

Those receiving tenure within the SOP are: Jochen Klein, Ph.D., associate professor, Department of Pharmaceutical Sciences, Amarillo; and Cornelis Van der Schyf, Pharm.D., Department of Pharmaceutical Sciences in Amarillo.

Thomas Abbruscato, Ph.D., was promoted from assistant professor to associate professor, Department of Pharmaceutical Sciences, Amarillo.

Non-tenure track faculty receiving changes in academic rank at the SOP include: Krystal Haase, Pharm.D., assistant professor to associate professor, Department of Pharmacy Practice, Amarillo; Brian Irons, Pharm.D., assistant professor to associate professor, Department of Pharmacy Practice, Lubbock; Rebecca Sleeper, Pharm.D., assistant professor to associate professor, Department of Pharmacy Practice, Lubbock.

We would also like to recognize our colleague at the School of Medicine (Amarillo): Rodney B . Young, M.D., was promoted from assistant professor to associate professor, Department of Family and Community Medicine.

Congratulations to you all!

NIH Announces Electronic Grant Submissions

Beginning with the small business grant programs on Dec. 1, 2005 and transitioning program by program through September 2007, NIH will require all competing grant applications to be submitted electronically through the federal on-line portal of Grants.gov (www.grants.gov) using the SF424 (R&R), a new standard form set created by federal agencies involved in research and research-related grant funding. All NIH grant applications- (new applications, revisions, continuations, renewals, AIDS and non-AIDS applications) will be affected by this transition. Once a grant program is transitioned, paper applications will no longer be accepted for that grant program.

This major change in the way NIH has traditionally conducted its grants business will have a significant impact on the applicant community. NIH has many resources available at its Electronic Submission of Grant Applications (http://era.nih.gov/ElectronicReceipt/) website to help grant applicants along the way. Applicant organizations are encouraged to:

- Review the transition timeline (http://era.nih.gov/ElectronicReceipt/strategy_timeline.htm) to determine when a research grant program of interest is switching to electronic submission.

- TTUHSC is already registered as an institution at Grants.gov; however, to register with eRA Commons, investigators must contact Lee Ann Paradise, Office of Sponsored Programs at (806)743-2960 OR Lee.Paradise@ttuhsc.edu **at least two to four weeks** before planning to submit an application.

- Familiarize yourself with the instructions for the new SF424 (R&R) in the application guide (http://grants.nih.gov/grants/funding/424/SF424_RR_Guide_General.doc) , especially the agency specific instructions.

Avail yourself of the training (http://era.nih.gov/ElectronicReceipt/training.htm) resources including slide and videotape presentations, brochures and upcoming training sessions.

Prepare for electronic submission. Stay informed.

PLEASE NOTE: NIH R01 grant submissions will need to be submitted electronically as of February 1, 2007 (an extension from what was originally announced).

Online Resource Highlighting Research Centers

The Higher Education Research Centers Inventory provides a valuable inventory of Texas higher education research centers that can be used by current and future Texas companies to build collaborations with universities and health-related institutions to develop new technologies that will lead to new jobs and an expanded economy. — quoted from the website at: https://www1.thecb.state.tx.us/apps/centers/

Investigators can search for centers by keyword, category, institution or cluster. The School of Pharmacy's three centers may be found here at this site, as well as on our own School webpage at: http://www.ttuhsc.edu/sop/research/InternalGrants/ResearchCenters.aspx

Upcoming Events/Deadlines

ABRI Program
Selected interns will begin their work on Monday, May 29 and will finish on August 4, at Research Days. Please welcome these students to our school!

Fifth Annual Research Days Event
Research Days will begin this year on Wednesday, August 2. The event will break on Thursday, August 3 for an all-day faculty grant-writing seminar. Research Days activities will resume and conclude on Friday, August 4.

Seed Grants for Fiscal Year 2007
Internal seed grant applications for fiscal year 2007 will be due **by 5 p.m. on Tuesday, August 15, 2006**. Please refer to the SOP OP 73.P.04 Seed Grant Program Policy for additional guidance: http://www.ttuhsc.edu/sop/administration/policies/73.P.04%20Seed%20Grant%20Program.pdf

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***Nucleus* is a quarterly newsletter published by the SOP Office of the Associate Dean for Research.**
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