



Bench to Bedside, Bedside to Bench

One Dose Doesn't Fit All: Evaluating the Magic Bullet

By Jessica Thorpe, Outside the Box Communications

Donald Mager and Brian Tsuji, UB SoPPS assistant professors of pharmaceutical sciences and pharmacy practice, respectively, agree: The time of the “magic bullet” is most likely over.

That doesn't mean there isn't new knowledge at bedside and bench waiting to be discovered—particularly as it relates to novel and individualized pharmacotherapy.

“We're beyond the days, I think, where we're going to develop the single drug for a single target that is going to knock out that target with a single dosing regimen for all individuals and achieve the outcome we wish to achieve,” says Mager, whose bench work has carved major PK/PD modeling inroads into the optimization of drug therapy for cancers and metabolic diseases.

At the bedside, Tsuji is on the front lines. “We're losing the arms race in the fight against resistant ‘superbugs’ and are investigating novel ways where we can optimize the activity of antibiotics,” he says of his clinical research in infectious disease, warning of the growing global threat from antibiotic-resistant pathogens.

In Hochstetter Hall, Mager approaches his laboratory research with the unique perspective of a former practicing pharmacist. “I actually earned my bachelor's degree in pharmacy, when you could get such a thing,” he laughs.

Originally from Albion, N.Y., Mager worked as a community pharmacist before returning to UB to earn both a PharmD degree (2000) and PhD (2002) in pharmaceutical sciences. After completing a postdoctoral fellowship at the National Institute on Aging, he joined the UB SoPPS faculty in 2004.

The six years he spent as a staff and supervising pharmacist with the former Fay's Drugs was a special time in his life, he says. “To be able to explain difficult concepts to the layperson, to actually translate science that would be meaningful to individuals, to me was really gratifying,” he says.

But he had gotten a good taste of research during an undergraduate rotation, investigating the relative efficiency of acetylcholinesterase isoforms and conducting functional assays for tacrine, the first FDA-approved drug for the treatment of Alzheimer's. “It was a glorious experience,” he says of defining a hypothesis and working with faculty member Harvey Berman and members of

his lab to test that hypothesis. “The career lifestyle of academic research was really quite appealing to me.”

After being accepted into the PharmD program, Mager landed a coveted graduate research slot with William J. Jusko, SUNY Distinguished Professor and chair of the Department of Pharmaceutical Sciences, looking at corticosteroids and interferon beta as model compounds that modulate the immune system. The effects of both drugs take time to develop because they cause changes in the expression of certain proteins and enzymes.

“The complexity between the exposure and the outcome of the drugs led to theoretical concepts that could be broadly applied to many compounds,” Mager explains. In 2001, he published his first two papers, describing the mathematics of time-dependent and target-mediated systems. “The modeling suggested that the drug binding to the target receptor influenced the time the drug spends in the body and also the effects that it elicits. Since then, there have been many drugs identified to elicit the same behavior. And the real expansion comes from monoclonal antibodies and proteins.”

His research remains focused on this principle of target-mediated drug disposition, a concept brought to light in 1994 by Gerhard Levy, SUNY Distinguished Professor Emeritus in SoPPS.

Mager now travels the world giving lectures on novel interpretations of the concept.

"Drugs always bind to a target to cause their response. But it's relatively new knowledge that that interaction influences how the body processes the drug," he says. "For select new drugs, binding to the target receptor influences the observed time course of the concentrations. This is what is unique."

Mager's current lab work, carried out with a team of four postdoctoral fellows, six PhD students, four master's students and one technician, is focused on anti-cancer and immunomodulatory drugs—drugs that alter the immune system response—with an eye still fixed on interferon beta, a drug used to treat multiple sclerosis.

"The thing we're really excited about right now in this field is the use of mechanism-based pharmacodynamic models," Mager says.

"We want to understand how physiology and drug properties together influence the time course of exposure and response. How do diseases, patient genetics, the environment (like diet and smoking), concomitant medications and other factors influence what we observe? The modeling allows us to bring all of these facts together into one cohesive unit to better understand what is influencing what we observe in terms of drug exposure-response and clinical outcomes," he says. "We're trying to understand how to optimize therapy in the presence of complex systems. We hope to eventually be able to personalize pharmacotherapy by appreciation for how the system is working."

Mager says modestly that his research—which is funded through NIH co-investigator grants, the UB-Pfizer Strategic Alliance, the UB Center for Protein Therapeutics and company-based sponsors—is in its "early days." This is true in general for PK/PD research as it relates to combination drug therapy, acknowledged as the wave of the future. But one of Mager's postdoctoral fellows, John Harrold, has developed an innovative mechanism-based pharmacodynamic model that predicts synergy for the anti-cancer drug rituximab in combination with other therapies.

"It's hard enough to optimize one drug. How does one optimize treatment with multiple drugs, each with its own mecha-

nism, and then interactions between mechanisms?" Mager asks. "What was exciting in this very preliminary mouse study is that we were able to take information from single drugs and actually predict the observed synergistic response—two drug combinations were actually more beneficial than just their additive sum effects."

From the clinical research perspective, Tsuji is looking at the potential of combination drug therapies that can be useful at the bedside and eradicate highly resistant pathogens, including staphylococcus aureus and pseudomonas aeruginosa. "Some strains have mutated to develop resistance to nearly all commercially available antibiotics. Our research on these two critically important pathogens focuses on using PK/PD, bacterial genetics and patient specific factors to optimize outcome," he says.

Tsuji says that his research, funded through NIH co-investigator grants, Upstate New York Consortium for Healthcare Research and Quality Foundation grants, the UB-Pfizer Strategic Alliance and company-based sponsors, is just starting to take off. "It is so exciting to work in a team of PharmD and PhD students, undergraduates, research scientists and PharmD and PhD postdoctoral fellows who are so truly motivated to research antibiotics in infectious diseases. It is because of all of their hard work, not mine, that we as a team have been able to do what we do. They deserve all of the credit for our research."

Part of his research team is looking at ways to preserve the usefulness of the drugs vancomycin and colistin. Both drugs have been in existence for more than 30 years and have been the last line of defense in the treatment of resistant gram-negative and gram-positive infections. These antibiotics recently have come under the gun because of potential issues of resistance and poor patient outcomes.

"At the bedside, we really don't have strong evidence, both clinically and experimentally, of how to optimally use these drugs, although they have been around

for decades. One area of research by Samira Merali (PharmD postdoctoral fellow), Dung Ngo (PharmD student) and Neang Ly (PhD student) looks at vancomycin and colistin in combination with a plethora of other antibiotics."

Tsuji earned his BS in pharmaceutical sciences in 2001 and PharmD in 2003 from Wayne State University in Detroit. After working as a clinical pharmacist at Detroit Receiving Hospital, he completed a postdoctoral fellowship at the Detroit Medical Center and Wayne State University, after which he joined the UB SoPPS faculty in 2005.

"As a student, clinical pharmacist and fellow, I was so intrigued by antibiotics and infectious diseases because of the huge impact that pharmacists could make on a medical team to improve the outcomes of patients. My early passion for antibiotics was driven by the fact that we could not clearly answer a number of clinical questions on medical rounds, which is why I chose to investigate some of them in a research setting," he says, adding that these include pharmacy-related questions about the right antibiotic, the right dosage and the right duration.

Tsuji, like Mager, relies on basic PK/PD principles and modeling, in collaboration with faculty members Alan Forrest and Jurgen Bulitta, to carry out his investigations. He and his research team of postdoctoral fellows, PharmD and PhD students, technicians and undergraduates utilize new experimental techniques that mimic human pharmacokinetics in a test tube to study human conditions and severity of a bacterial infection.

"We use novel in vitro pharmacodynamic hollow fiber models to determine the most optimal way to administer antibiotics to prevent resistance," Tsuji explains. "One of our most recent papers was titled 'Implications for dosing in pneumonia,' so we

try to attack clinically relevant issues that can be brought back to the bedside."

Toward this scientific end, his research seeks to understand heterogeneous resistance for vancomycin and colistin among "flip-flopping" phenotypes—bacteria that actually adapt and mutate in the face of drug therapy. "It's similar to the tip of an iceberg, where everything appears normal on the surface. However, after suboptimal drug therapy, the whole population of bacteria can mutate and become resistant, which presents a serious problem," Tsuji says. "These bacteria have been called 'Jekyll-and-Hyde' organisms because they show different faces and change depending on their environment—from the non-threatening staph in your nose to causing very severe infections, such as bacterial endocarditis or necrotizing pneumonia."

Working both in Cooke Hall and at UB's New York State Center of Excellence in Bioinformatics and Life Sciences on the Downtown Campus, Tsuji also looks at bacterial genetics to find ways to more effectively treat patients.

The general theme for both bacterial pathogens he is working on is that they can adapt to drugs and to their environment by communicating with each other. Consequently, Tsuji is investigating the role of bacterial quorum sensing in the development of drug resistance and how it also may contribute to severity of infection. At least one of the quorum-sensing genes that relate to bacterial crosstalk causes resistance in vancomycin, the former "magic bullet" drug for treating staph infections, he says.

"If we could potentially use drugs that target these genes, we can be very aggressive at individualizing therapy to use single or combinations of drugs differently."

Tsuji collaborates with six different hospitals—from Albany to Rochester to Buffalo—to determine the prevalence of vancomycin-resistant phenotypes and what can be done to treat these infections. Like Mager, he shares his research in national and international lectures to fellow scientists and scholars.

The buzzword these days is individualized or personalized medicine, both Mager and Tsuji say. "If we have a model that we think explains how the system is functioning, then we can look for patient covariates, individual characteristics that explain why one individual is responding differently than another individual. And I think a model-based approach will really provide the best path for the individualization of therapy," Mager says. Tsuji smiles when hearing of Mager's comments, agreeing, "It is true: One dose doesn't fit all."

