At the bench, Dr. Nguyen is creating a novel intercellular 'zip coding' approach for cancer and heart disease treatment.

BENCH TO BEDSIDE, BEDSIDE TO BENCH

SPPS junior faculty members with planetary vision are piloting pharmaceutical science and clinical pharmacy toward healthcare horizons to come.

WITH JUST THREE YEARS EACH AT UB, Juliane Nguyen, PharmD, PhD and Christopher Daly, PharmD, MBA, are leading novel research and practice innovation that is redefining the interdisciplinary scope of their individual areas of focus, as well as the collective disciplines of the entire pharmacy field.

In pharmacy practice, clinical assistant professor Daly is leading partnerships in pre-study, study and post-study clinical pharmacy research that will help patients better manage chronic and acute medical conditions; assistant professor Nguyen is at the bench in pharmaceutical sciences, providing hope and new insight into treatments for cancer and heart disease.

In the therapeutic biomaterials laboratory, Nguyen is investigating bio-inspired drug delivery methodologies to improve therapeutic efficacy.

"There are really good drugs out there. But there are diseases that can still not be treated. They are incurable. We are focusing on designing better biomaterials that are drug delivery carriers to address these shortcomings," she says.

As a high school student in her national Germany, Nguyen gravitated to the natural sciences and was fascinated by chemistry.

"At that time my understanding of chemistry was limited to small molecules. I didn't know it could be used to engineer or synthesize biomaterials," she recalls.

Her parents' dream for her was of a career in retail pharmacy: She earned her PharmD and then a PhD in pharmaceutical sciences – with a focus on the design of biodegradable polymers for nucleic acid delivery – from Philipps University in Marburg.

Discovering a passion for research, Nguyen applied and was accepted as a post-doctoral fellow at the University of California at San Francisco with Francis Szoka, PhD.

"He is one of the pioneers in liposomal drug delivery and one of the first to bring a lipid formulated drug onto the market. He was also a founder of Sequus Pharmaceuticals that developed the Doxil anticancer formulation that is now sold by Johnson & Johnson," Nguyen says of her mentor.

"This post-doc position was invaluable in that it shaped the way I now think as a scientist." As a scientist, Nguyen's investigative vision is clear and profoundly galvanized by

At the bedside, Dr. Daly leads an innovative research pharmacy focusing on unique, outpatient, investigational drug studies.

her love and understanding of natural science – its sophisticated mechanisms orchestrate a myriad of complex tasks, and inspire hybrid paths for creating better synthetic or bio-inspired, drug delivery systems.

"We can learn from viruses, cells and bacteria. Synthetic polymers and lipid nanoparticles are good, but often not as efficient as the natural systems. Because the natural systems have evolved over millions and millions of years they are really good at what they do. So we can learn from them," she says.

Nguyen's research work is focused on the design of smaller biological carriers that are recognized by the biological system.

"We are particularly interested in molecular zip codes," she explains, using a post office metaphor to explain her novel investigation into intercellular communication. "A city has a lot of buildings. Each has a name, an address and a zip code so the mailman knows exactly where to bring the mail. If the information is missing they don't know where to deliver the mail.

"That's the same way biomaterials or drug carriers work in cells. If you put something into a cell and the cell recognizes it as foreign, the cell either doesn't know what to do with it or uses a mechanism to eliminate the foreign subject."

Her "zip codes" are defined by experimental methodology – intensive library screening to identify sequences that act as zip codes. Using Polymerase Chain Reaction – a powerful scientific method performed with a small piece of equipment used in molecular biology to render precise biomaterials – Nguyen genetically reprograms cells to perform specific tasks.

"We treat cells with zip code-like materials and the cells know exactly how to process that nucleic acid or any other therapeutic drugs delivered by those materials. We're really interested in having these nucleic acids sorted to exosomes."

Exosomes play a critical role in cellular communication, and contain genetic information that allows them to manipulate or modulate their environment. They can contribute to the progression of neurodegenerative disease, autoimmunity and cancer; once secreted by a parent cell, exosomes are captured by neighboring cells or released into systemic circulation for uptake by distant tissues and organs.

"We try to understand the natural systems better so that we can manipulate them to exert a specific function that will stop disease progression," Nguyen says.

In cancer, the lipid, protein and nucleic acid content of exosomes are known to promote metastasis. So Nguyen is reprogramming cells with zip code-like materials that tell exosomes to target a specific site and perform very specific functions.

"By introducing the zip codes into the cells and attaching a therapeutic drug to them, the drug gets loaded into the exosomes because it knows not to go to the nucleus or other parts of the cell: This therapeutic cargo takes charge..." she explains.

"I have very hard-working students in the lab," she smiles. "What I learned during my post-doc was to think outside of the box. That's what I try to teach them too, because that's one of the best ways to discover better drug delivery vehicles, to advance the field."

"We have lipid nanoparticles and we have these sequences that we encapsulate in them. We place them into the cells and the zip codes tell them where to go."

Nguyen has theorized that this novel zip coding platform for sorting therapeutic cargo to exosomes will increase the efficacy of drug delivery and ultimately improve therapies for – or potentially cure – a range of difficult to treat disease states, including heart disease.

"We haven't done this *in vivo* yet. We are planning to go in that direction, but just the discovery of these zip codes is potentially huge. We are in the process of filing a provisional patent," she says.

In addition to targeting cancer, she is investigating the use of macrophages as biological drug carriers to treat myocardial infarction.

After a heart attack the cardiomyocytes in the area that is blocked from blood flow and oxygen die and are replaced with cells that don't have the ability to contract. Nguyen wants her zip coding, exosome sorting technology to make cardiomyocytes self-renew and multiply.

"Our goal is to use inflammatory cells as drug carriers. After a heart attack the inflammatory cells go to the site of the infarction. We want to use them to secrete a protein that makes the cardiac cells divide or self-renew. In this case, the delivery vehicle is the cell that migrates there and the protein is the drug."

Nguyen's work with myocardial infarction is carried out in collaboration with SUNY Distinguished Professor John M. Canty Jr., MD. In Kapoor Hall, she directs an interdisciplinary team of two pharmaceutical sciences students, a chemistry post-doctoral fellow, two biomedical engineering students and several undergraduate students. Her research is funded by the National Institutes of Health, the National Heart, Lung and Blood Institute and the National Institute of Biomedical Imaging and Bioengineering.

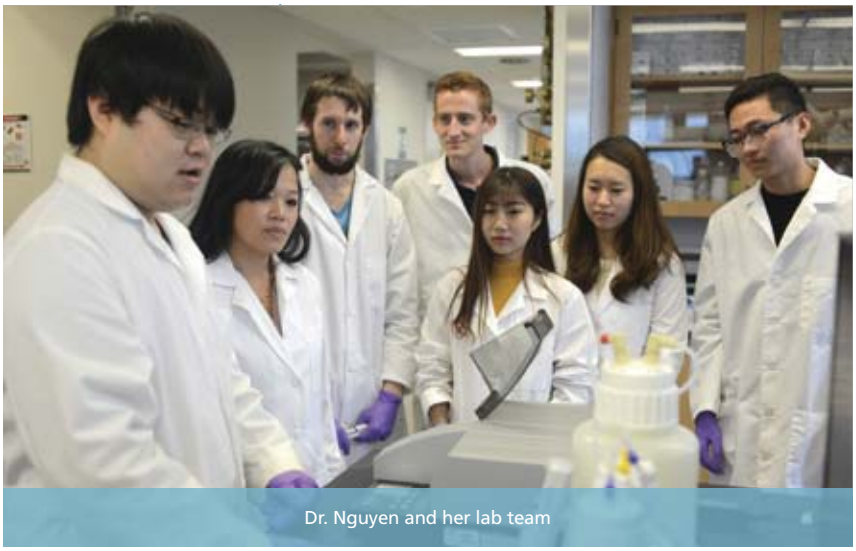
"I have very hard-working students in the lab," she smiles. "What I learned during my post-doc was to think outside of the box. That's what I try to teach them too, because that's one of the best ways to discover better drug delivery vehicles, to advance the field."

At the lectern, assistant professor Nguyen teaches a class on drug development and a section of a drug delivery class focused on nucleic acids and bio-inspired materials. She also teaches disperse systems and drug formulation in Physical Pharmacy.

Like Daly, she too envisions that the impact of her bench work using biology techniques to reprogram exosomes will extend far into the future.

"We envision that our zip code-like biomaterials could be used for the treatment of cancer metastasis. Being able to interrupt pathological cellular communication is a big step," Nguyen says.

"In the case of myocardial infarction, there is currently, besides heart transplantation, no treatment that completely regenerates the heart. There is no treatment that fully cures the disease. So this is what we are aiming to do."



Dr. Nguyen and her lab team

Christopher Daly, through the UB SPPS Research Pharmacy, is working to advance the pharmacy practice field with a model to centralize delivery of the pharmacy support needed to carry out clinical studies that are increasingly interdisciplinary.

"An investigator comes to us when they want to do a clinical study, consisting of medication-related human subjects research, and have a specialized need for dispensing or other pharmaceutical need," he says of the Kapoor Hall Research Pharmacy where he is the principal investigator.

"They need help getting product to the patient in a way that is going to improve adherence, maximize safety and augment the outcomes of what they investigating."

Daly earned a dual PharmD - MBA degree from SPPS in 2012, and went on to a Post-Graduate Year 1 Community Pharmacy residency at the University of North Carolina Eshelman School of Pharmacy and Moose Pharmacies, near Charlotte.

"It was a very progressive and innovative environment, very different from New York. There were aspects of community pharmacy but we also performed clinical functions for a centralized Medicaid managed care organization, Community Care of North Carolina.

The Research Pharmacy Team

We would work on patient cases that needed a pharmacist to look at the medication lists coming out of the hospital, and determine if there were drug therapy problems consisting of high risk medications, non-compliance or duplication of medications," he says.

"There were a lot of parameters that would involve our expertise. Pharmacy practice is moving forward at this present time. It is becoming more clinical… more population focused in addition to bottom line, volume driven services. The future will look to assimilate these sometimes competing key drivers."

When Daly returned to UB to join the faculty, he was tasked with the innovation of practice opportunities for advanced clinical pharmacy research and now leads the strategic, service-driven development of UB SPPS Research Pharmacy.

What is now the SPPS Research Pharmacy evolved from an entity that was defined in 1995 as a result of investigator-related compliance issues. On the South Campus, it provided support for studies that included nationwide clinical trials for medications used to treat ADHD.

"It started as an invention to fill a need for more pharmacy support in clinical research. Investigators needed pharmacy involvement from a regulatory point of view. Now the vision here at UB is to centralize research in one area at the Clinical Research Translational Center. When we centralize there we can grow exponentially with them," Daly explains.

Located in the Buffalo Medical Corridor near downtown, the CTRC serves as an integrated academic home for outstanding clinical and translational science, providing innovative research tools, support, training, resources and coordination. The CTRC is the hub of the Buffalo Translational Consortium (BTC) formed in 2009, which includes the leading academic, healthcare and research institutions in the Buffalo region, along with key community partners. Each BTC institution is represented in the governance of the CTRC.

With dual training in business administration and pharmacy practice, Daly is responsible for coordinating the day-to-day activity and strengthening the internal processes of the SPPS Research Pharmacy. He also serves as its liaison to the University at Buffalo Research Foundation, which has oversight on how its funds are collected and distributed.

"We are a closed door New York State outpatient licensed pharmacy. You can't bring a prescription to us and have it filled. That's the simplest definition of what we are," he explains.

"We only dispense according to Institutional Review Board protocols and New York State Board of Pharmacy regulations. So we operate on a scientific and proprietary plan with a principal investigator, with principal investigators from all over the BTC. When you look at the caliber of who we provide service to, you understand why UB is recognized as the research leader that it is here."

The SPPS Research Pharmacy self defines as a "unique, outpatient, investigational drug pharmacy" with a population limited to patients who are enrolled in clinical trials. It provides clinical trial support for UB-affiliated investigators from all of the UB Health Sciences schools, as well as to PhD and masters degree candidates from various departments who are working on research projects. Evolving outreach includes all the clinical institutions and community partners that comprise the Buffalo Translational Consortium as well as interested campus partners at the University at Buffalo.

To define the scope of pharmacy support for a clinical study, Daly designed a comprehensive Research Medication Services Request Form that itemizes the broad range of services which include, among others: special packaging and patient instructions for complex dosing regimens, randomizing and blinding, placebo preparation, adverse reaction monitoring, maintaining patient logs and dispensing records, patient counseling on medication-related issues, and organizing and analyzing study data.

"We partner differently for every study, depending on the investigator's focus. Some studies are investigator initiated and some are initiated by a pharmaceutical company," he says, adding that the Research Pharmacy also provides post-market analysis.

"We also work with clinicians who are trying to maximize the use of existing drugs. These drugs may be already FDA-approved for one treatment, but need a New Investigative Drug application to be used for another treatment."

Like Nguyen's hybrid bench work with bio-inspired drug delivery, Daly ultimately is developing a hybrid business-practice model to lead the future of research pharmacy. Currently, the SPPS Research Pharmacy manages approximately 25 studies – and he is focused on increasing that number. Funded now primarily by the contracted services it provides, Daly also is focused on building support for clinical pharmacy research directly into an investigatory grant.

Other advancement objectives include expanding pharmacokinetic, pharmacodynamic and pharmacogenetic capabilities; establishing Kapoor Hall as a clinical site and collaboration with the Research Institute of Addictions.

"We're at a really good point where we're maximizing our operations and abilities here, and beginning to strategically add new evolutions to our model to get to the next step, whether that's new equipment, such as a tablet press machine, or to become USP 797 compliant, with the ability to make sterile preparations to dispense to human subjects," he says.

In keeping with the SPPS mandate of academic excellence, both Daly and Nguyen also are preparing the next generation of pharmacy practitioners and pharmaceutical scientists to advance the novel work they have begun.

"We teach all the time," says Daly, whose teaching passion lies in the social and behavioral sciences aspects of pharmacy practice management, entrepreneurship and innovation.

"We have students with us, on rotations. We teach them good clinical practice through research pharmacy and really impart to those who are interested in a research focus what it is that a research pharmacist does, and how they are able to align with studies and be a part of a research cycle."

The continued evolution of the SPPS Research Pharmacy, he says, potentially will improve the future of patient care by expanding the scope of support available to clinical investigators.

"I believe it's going to give investigators a bigger toolkit that allows them to imagine and design more complex and effective studies. UB is expanding out to be a state-of-the-art research facility and the SPPS Research Pharmacy I would like to believe is a very exciting part of that."

J. Thorpe, Outside the Box Communications