STUDENTS GET READY FOR A LIFETIME OF DISCOVERY

BY REBECCA SKLOOT

AS EYES ADJUST TO THE DARKNESS

Anh Lam, MD '03, stands on the 10th floor of the Biomedical Science Tower, staring apprehensively at a floor-to-ceiling black cylinder, just large enough to hold a person.

"That's the scary black revolving door," she jokes. "I'm always afraid I'm going to get stuck." With a deep breath, Lam, who just finished her first year as a University of Pittsburgh medical student, steps inside the tube, grabs a handle, and rotates the walls around her until she is in a nearly pitch-black room. As her eyes adjust to the darkness, a red halo of light directs her toward the film developer in the corner. It groans as Lam inserts an undeveloped film of gel electrophoresis. She has worked in a few labs (has even conducted her own projects at the National Institutes of Health), but this is the first time she has done this particular technique, called the electrophoretic mobility shift assay (EMSA), so she is eager for the results. Yet, with arms folded, she can only wait.

Jennifer Grandis (left) and Anh Lam

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FROM LEFT: Susan Manzi, Chris Thunberg, and Joseph Ahearn spent their summer talking a lot about lupus. Manzi is an MD/MPH and, though not formally part of the summer research program, volunteered to take Thunberg into the clinic to see lupus from that perspective to complement Ahearn's work with him in the lab.

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Lam is one of about 30 medical students who spent their summer vacations in research laboratories through the Medical Student Summer Research Program at Pitt. The program, which has been around since the '60s, lets physicians-in-training experience the research side of medicine, working closely with a faculty mentor. With the forecast for the next generation of physician-scientists looking meager in terms of numbers, the program hopes to inspire some students to pursue research careers, but by no means is that the program's only goal.

"Research experience is just as important for students who will go into private practice," says Stephen Phillips, associate dean of graduate studies and director of the program. "As physicians, they're the beneficiaries of discovery. They prescribe drugs or procedures whose origins are in scientific research, and they need to find out from personal experience what discovery is all about." So for eight weeks, students pair up with faculty mentors to collaborate on a research project.

Anh Lam got a good dose of discovery this summer. In addition to working on two research projects, she watched her first surgery, and found herself in exam rooms observing doctor-patient interactions. On top of all this, Lam got to work alongside Jennifer Rubin Grandis, associate professor of otolaryngology and pharmacology.

Grandis thinks part of her job as a mentor is not only to guide students in conducting research and foster their excitement for science but to show them they shouldn't underestimate what they can accomplish, professionally and personally.

"My hope," says Grandis, "is that some of these students will get turned on enough that someday they'll think, *Oh yeah, I can do [that]. She had a family, saw her kids, wrote grants and papers, took care of her patients, and even baked muffins.*"

Grandis (MD '87) was a mentee in earlier years of Pitt's research program—and she doesn't mince words in describing her experience: It was horrible. She spent the summer avoiding what she calls "the French Revolution thing." Alone in a laboratory with cages and cages of rats, Grandis was charged with decapitating them for endocrine studies. "The only thing I remember about that summer," she jokes, "is that I bribed a technician. I paid her my entire stipend to kill those rats for me. It didn't inspire me to go into science."

Phillips remembers Grandis's experience well, and he shakes his head as he tells the story. "Not everyone can be a good mentor for this kind of project: a compressed, very well defined, summer of intensive direction." But Phillips has learned a lot in his 30 years of involvement with the program. He has a network of colleagues that he depends on for pairing students with the right mentors.

"That first experience is the most crucial in the life of a serious student who wants to explore whether research is for them," he says. "You can wreck them for life if you don't do it right." Fortunately, Grandis went on to find other mentors, and now her life revolves around science. But her first experience took a toll, and she wants to make sure that doesn't happen to her students. So each mentee who comes through her lab is given a project to investigate alongside others—usually residents, postdocs, undergraduates, and several technicians. Grandis makes sure Lam and other program participants do original research.

Lam spent part of her summer working on a phase-one gene therapy trial for treating squamous cell carcinomas of the head and neck. She spent countless hours extracting DNA from animal tissues and checking for localization of the therapeutic gene to determine whether it stayed in the area where it was injected. The rest of her time, Lam worked on the EMSAs she developed in the darkroom behind the black revolving door. These gels will be used as a tool for determining the activity of proteins that regulate genes that may be important in cancer development. With these EMSAs, Grandis's lab hopes to develop methods for blocking the activation of cancer-causing genes.

Before Lam braved the black revolving door, she jerked open a freezer kept at -80 degrees Celsius and pulled out a film cartridge about the size of a notepad. "This is the first time I've done this particular technique," she said, brushing ice crystals from the plastic and rotating the cartridge in the air, as though it offered clues about the gel inside.

It's an everyday occurrence in labs everywhere, but it's also a moment of bated breath and expectation. The results of this EMSA will help Lam decide where to take her project from here. With each answer unveiled, a researcher, such as Lam, advances her knowledge an increment forward, opening up new questions that can keep her going in the same direction, or pointing toward completely new paths.

The same is true for good clinicians doing diagnostic work.

"Research is about asking questions of the unknown," says Phillips, "and designing experimental systems that will provide answers.

"So does that make it a fact?" he'll ask. "On what was the statement based?"

Don't blindly accept anything as truth, he tells students, without first seeking evidence that supports it.

"Sometimes these things can be traced back 20 or more years to show that no one has done an experiment in decades to revise what has been said," he explains. "So being a good investigator isn't just about asking questions, but questioning what supposedly is truth and realizing that maybe there's another explanation."

That's hitting home for Chris Thunberg, MD '03, who's working with Ahearn this summer. Three floors down from the room where Lam stands blanketed in darkness waiting for her gel, Thunberg stands at his meticulously organized lab bench. The soft sound of clinking glass is muffled by the hum of industrial freezers as Thunberg washes tissue samples he hopes will shed light on the autoimmune inflammatory connective tissue disease known as systemic lupus erythematosus.

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"The art of differential diagnosis involves knowing the questions to ask that enable you to arrive at the likely cause of disease." In the laboratory and the clinic, successful investigators don't just ask questions—they ask answerable questions.

"Asking the unanswerable question may be good cocktail party conversation," he says. "However, in terms of the day-to-day life in the laboratory or in the clinic, asking the answerable question is the key."

In addition to asking the right questions, students in the program learn that the answers should be questioned as well.

This is a sticking point for Joseph Ahearn, associate professor of medicine and one of the program's mentors.

"Students often come in to start a project and recite what they consider a fact," says Ahearn. He outlines a typical example: A student tells him what she thinks causes lupus. He'll look at her and say, "Well, how do you know that?"

"It's in the textbook," she'll say, or in a peer-reviewed article.

Thunberg's project funding is the result of a national competition sponsored by the American College of Rheumatology. That funding has enabled him to augment his summer experience by working with Susan Manzi, an MD/MPH, this fall. In that phase of the project, he'll gain experience with lupus from a clinical perspective.

He is getting a good feel for what makes for a successful career as a physician scientist.

"Working with Dr. Ahearn," says Thunberg, "it's clear that one requirement is thinking outside the box."

"Take lupus," he says. "Lupus patients get UV-sensitive skin rashes on their faces. Dogma says that these rashes are simply manifestations of the disease. But the experiments we're doing might show that UV light damages the skin in a way that triggers lupus and causes the rashes to happen."

Ahearn remembers when he first caught the research bug. For him, there was no formal introductory program; and it came well into his education, after school, internship, residency, and fellowship.

"It was the rush of the scientific process," he says, "realizing that you're in a position to discover something no one else knows—that you could come out of a darkroom in the middle of the night and realize that you just discovered something brand new. It's just incredible."

Even if Thunberg doesn't follow Ahearn's lead and pursue a career in academic medicine, his lab time will pay off down the road. Says Phillips: "The life of a physician is a life of discovery."

Lam stands in the darkroom anxiously awaiting her film. Time seems to be standing still. During the lull she chats with the laboratory technician, Kevin Dyer, a.k.a. "Farmer Kevin," the technician in beige overalls who has surprised her with a cup of espresso. Her colleague will help her reconfirm what is and isn't important: As Dyer and Lam discuss the experiment, he points out they are not trying to "find" a particular result.

"That's not the way you look at it," he says. "With research, you let your data do the talking." Lam nods in agreement. This has become almost a mantra for them in the lab today.

"You don't go into it with the notion that this is the result you want," he says, "because you're going to bias your interpretations. You might just see the result you want."

The conversation ends abruptly when the film hits the tray beneath the developer. Lam grabs it and holds it to the light.

"What do you see?" asks Dyer. They move into a huddle with the film between them.

"Check it out," says Dyer, "this is a band that's higher than the ones we've seen."

"Does that mean it bound better?" wonders Lam.

"It means different," he replies.

The two lean in and go over every detail on the film. One result isn't what either of them expected.

"I don't know what to make of this one," says Dyer. "It's a trip."

They talk about new directions for the experiment that might shed light on this surprising result. Lam is eager to pursue the finding. She talks passionately about further studies. And she thinks about her mentor, then rushes to the black revolving door.

"Do you know where Jen is?" she asks, full of excitement.

"I want to show her this. I know she'll want to see it." ■