PhD student Adelajda Zorba is studying at the most fundamental level what might spur cancers. Using the latest NMR technology, she says, "is as close to the truth as I can get." (Shown here: part of the structure of the aurora-A kinase molecule, which may be a culprit in a variety of cancers.)

IMAGE COURTESY D. FANCELLI ET AL. MODIFIED BY A. ZORBA

THE INVESTIGATOR'S PATH

PITT'S PHD PROGRAMS RAMP UP

BY JOE MIKSCH

A few words of advice for those who have urgent business to attend to at the Thomas E. Starzl Biomedical Science Tower when the Biomedical Graduate Student Association (BGSA) has its October research symposium and poster exhibition:

Rearrange your schedule.

Regardless of your intentions, if you walk through the Starzl Tower on that day, you are likely to be sucked into a vortex of more than 125 young PhD-seeking researchers eager to share the details of their budding careers. The enthusiasm of these earliest of early-career investigators is seductive.

Christi Kolarcik

CAMI MESA

bench scientists—especially those looking to find answers in the lab that have significance for patient care in the not-too-distant future. About one-third of the 875 or so students in Pitt's School of Medicine are pursuing PhDs—more than twice as many as a decade ago. To say that graduate training at the school is burgeoning is almost an understatement.

As this reporter enters the Starzl Tower lobby on a warm October day, students share news of their discoveries with one another amid a warren of posters. Angela Pardee—an enthusiastic third-year immunology student—notices my pause by her display. She pounces.

"I'm working on how costimulatory therapy can induce tumor rejection," she says, before outlining the process by which the administration of two recombinant cytokines (a kind of signaling compound) caused antitumor T cells (vanguards of the immune system) in mice to be more effective, halting and, in some cases, reversing their sarcomas.

"It looks like we can break immune tolerance to tumors, and that's the first thing we're looking for," she says, adding that the ultimate goal of her research is to develop a new cancer therapy.

"I'm really interested in translational research," she says, using the jargon for investigations focused toward developing new treatments.

The lesson concluded, this reporter walks away. Then, a few steps later, second-year molecular virology and microbiology student Abigail Boster approaches. She is investigating the role of microRNA in human papillomavirus–caused head and neck cancer. The cycle of friendly, impromptu education repeats.

The school's Interdisciplinary Biomedical Graduate Program, whose students are part of the BGSA, represents about two thirds of the School of Medicine's 279 grad students. The rest are pursuing their PhDs in one of five other disciplines: biomedical informatics, neuroscience, integrative molecular biology, molecular biophysics and structural biology, and computational biology.

Two of these programs—molecular biophysics and structural biology, as well as integrative molecular biology—are in their infancy, having hatched in the past few years. A seventh program, in clinical and translational science (made possible by a five-year, $83.5 million National Institutes of Health grant received in the fall of 2006), is on its way to the birthing room.

The School of Medicine has been bestowing PhDs since the 1950s, says John Horn, associate dean for graduate studies and a PhD professor of neurobiology. But of the 500 or so PhDs Pitt has granted, more than 40 percent have been earned in the past seven years, he says. Horn adds that PhD programs have been growing nationwide, but Pitt has made a concerted effort to lead the pack.

"There are some things we're doing that aren't unique," he says. "Having an umbrella program in the form of the integrated biomedical graduate program isn't unique, but we've had it as long as anyone. We bought into it early." On the other hand, Pitt's Program in Integrative Molecular Biology—which pairs the School of Medicine with the School of Arts and Sciences—is a rare bird, taking students who've had enough investigative experience for them to jump feet first into the study of the most basic biology.

Also, Horn says, the new joint Pitt–Carnegie Mellon University PhD Program in Computational Biology is sort of a reward for paying attention to trends in science: the creation of a novel discipline.

"Students are what virologists might call a 'vector.' They take an idea from one part of our community and express it somewhere else."

So you really should just plan on setting aside some time to learn about the remarkable things these students are thinking about.

These budding basic scientists may not be the type of student that immediately pops to mind when one hears "University of Pittsburgh School of Medicine." The white coat ceremony, anatomy lectures, rotations, and residencies: This is the path of the medical doctor, but it's not the path of every student at the school. Wait—med schools produce stethoscope-wielding, tongue-depressor-brandishing doctors, don't they? Of course, but as Pitt continues pursuing its mission to mold clinicians, the School of Medicine has also placed increasing emphasis on forming

“This is a field that includes neurobiology, structural biology, pharmacology, biochemistry, and genetics,” Horn says. “People have taken this [inclusive, cross-disciplinary] approach before, but now it’s emerging as a new, freestanding discipline.” Codifying the field, Horn says, will help Pitt PhD graduates rank among the best equipped to solve biological problems through computational methods.

Wishwa Kapoor, an MD/MPH who is Pitt’s Falk Professor of Medicine and chief of the Division of General Internal Medicine, explains that Pitt’s graduate programs emphasize translational and cross-disciplinary education because the questions being asked by biomedical science are considerably more complicated than they ever have been.

The easy, within-a-discipline questions have been answered, says the man who will lead Pitt’s embryonic program in clinical and translational science. To study the genetic links to congestive heart failure, a researcher would need expertise in cardiac disease, genetics, the lab procedures necessary to analyze genes, and statistics. Although one researcher may not be able to have expertise in all these areas, Pitt’s graduate programs encourage discipline-hopping even as students develop specialties.

The demand for institutions to inculcate basic scientists with the skills necessary to translate their work to the clinic, Horn says, is another factor that’s driven the growth of Pitt’s graduate programs.

A handful of colleagues, Horn reports, have said that perhaps their labs could make quicker progress if they worked exclusively with postdocs or researchers at the beginning of their independent careers rather than students. He disagrees.

“First of all, our mission is that of an educational institution,” he says, “but it makes for a much more vibrant intellectual environment, a more productive one, to have people at different stages of development working together.”

“Students,” Horn says with a laugh, “are what virologists might call a ‘vector.’ They take an idea from one part of our community and express it somewhere else.”

After Pardee and Boster explained the ins and outs of their research projects, it’s time to track down Christi Kolarcik, a member of the symposium planning committee. I want to learn who might attempt to corral all this intellectual energy while learning a bit about Kolarcik’s own.

Adelajda Zorba

CAMI MESA

As an undergraduate at Penn State University, Kolarcik was immersed in the world of chemistry. She wanted to go to grad school. Logic dictated that she consider chemistry programs. An undergrad professor suggested she look at Pitt. And she did, though something other than chemistry caught her eye.

“As I was researching programs I found out that I was interested in the translational [that bench-to-bedside] aspect of science,” she says. “I decided I didn’t just want to be in the lab and find out something about a protein and say, ‘That’s great!’ I wanted a program where I could find out what that protein means in the big picture.”

With its university-affiliated hospitals, broad and deep research programs, and expansive clinical network, Pitt’s Interdisciplinary Biomedical Graduate Program lured her.

Kolarcik enrolled in 2004 and hopes to complete her PhD in cellular and molecular pathology in May 2009. Her mentoring professor is Robert Bowser, a PhD in the department of Pathology and Neurobiology whose lab focuses on neurodegenerative diseases, especially amyotrophic lateral sclerosis (ALS). She’s done with classes and has passed her comprehensive exam but still participates in journal club, researches ALS, is learning to craft scientific papers and apply for grants, and, at this moment, shepherds her fellow poster-presenting students. She is busy. This becomes clear when, shortly after this reporter meets her, she seems to disappear into the ether—apparently there’s work to be done out among her peers.

Later on a less hectic day, in Bowser’s lab, where she spends more than 40 hours a week, Kolarcik is in the company of several glass slides containing thin cross-sections of spinal cord. Her omnipresent iPod is turned off in deference to her visitor. With speed and precision, she places the slides into a xylene bath, which erodes the paraffin coating on the sections; sets a timer; and changes her blue latex gloves.

She then grabs a set of slides that have been through the saline treatment, outlines them with a special pen that creates a kind of moat that will hold a solution containing an antibody she’s studying on the slide. She dips the slides into a bath that will block antibodies she’s not interested in from interacting with the sample.

She sets another timer. “Without these, I’d be lost,” she says. “My world revolves around timers.”

As the digital clocks wind down, Kolarcik explains her latest project. Some of her slides, taken from the ALS Tissue Bank—which her adviser, Bowser, directs—are from people who suffered from a familial form of ALS. Others are controls who died from non-ALS causes.

She's looking to sort out the difference between how a particular protein—retinoic acid receptor beta (RAR-beta)—interacts with the nucleus of motor neuron cells in each population. It turns out that RAR-beta is present in the nucleus of motor neuron cells in both ALS patients and the control group, but it's much more abundant in the former. Kolarcik and Bowser think that may contribute to cell death and the progression of ALS. Controlling RAR-beta, they suspect, may help ameliorate ALS.

What's exciting about the work, says Kolarcik, is that there's already an FDA-approved RAR-beta-related drug for cancer that could hold promise for ALS. Kolarcik is a bit coy about going into further detail.

"I want to be first," she says, with a smile.

"ALS, I think, has a researcher in me for life," she adds.

"Being in this building is like being at a conference. Everything is here, and it's up to you to take advantage of it, to exploit the opportunities."

While it seems Kolarcik has narrowed down her field of research, she says that the cellular and molecular pathology program within the Interdisciplinary Biomedical Graduate Program is, itself, far from limiting.

"One of the best things about Pitt is that a lot of people here do whatever they can to minimize barriers," she says.

In that way, the program welcomes both the highly focused student and the seeker. Those who are certain that they want to study a particular disease course or a particular protein, Kolarcik says, are introduced to a variety of techniques, disciplines, and colleagues that help open them to creative approaches to solving the scientific problems they encounter. These same elements, she adds, help the student who, though he knows he's interested in, say, neurobiology, refine his quest by encouraging him to sample a wide range of experiences.

Kolarcik has taken classes related to cancer biology, neurological disorders, and regenerative medicine and says, "The classes are related to your research, but they're related to other fields of research as well. Our program is excellent at encouraging students to think outside their disciplines."

Kolarcik's desk sits in a narrow lab space closed off by doors at each end. To her, it's almost a metaphor for how scientists work: alone and in teams. She has the privacy required to focus, she says, but has access to all the other inquisitive minds in the Bowser lab, the Starzl Tower, and the attached hospitals.

"I can sit down quietly and read a [scientific] paper, or I can walk across the hall and say, 'Hey, guys, what's up?' I can leave the lab to ask clinicians what they're interested in. It lets you know you're not working in a bubble," she says.

"The physicians and scientists are all, essentially, in the same buildings here," she adds. "I can just as easily talk to someone with a PhD as someone with an MD. If I'm working on some disease, if I want to get the physician's perspective, all I have to do is walk down the hall and ask, 'What would be valuable to you?'"

Horn says that's not an accident.

"It has taken a sustained effort, but we have a commitment to building community and to providing resources," he says. "We encourage people to cooperate, and we try to ensure that teamwork is a special feature of our environment here. Science is a battle of ideas. The first goal is to discover important things, and the second part is to reach people—to convince them that what you're doing is important. That breeds discovery."

The University's ample resources, in terms of equipment and people, says Adelajda Zorba, are what drew her to the School of Medicine's fledgling Molecular Biophysics and Structural Biology Program, which is a joint effort with Pitt's School of Arts and Sciences and Carnegie Mellon University.

A desire to spend a summer in France also played a role.

In 2005, Zorba was a junior at Colby College in Maine. As a chemistry/French double major, she needed to spend a semester in France to fulfill requirements for her bachelor's. Like many who visit Paris, she was charmed by the city and decided that she wanted to stay a while longer than the end of the term.

She found out that Colby would extend her stay if she were to find an internship. She called on the Pasteur Institute and was offered a two-month gig in a Nuclear Magnetic Resonance (NMR) lab.

"It was completely different from what I was doing on my organic chemistry track," she says.

At Pasteur, Zorba was assigned to use NMR, which employs magnetic fields to divine the structure of molecules, to develop an image of a small peptide.

"It was a simple project," Zorba says, "but I very much looked forward to going to work each day." She was hooked on NMR. She asked her adviser at Pasteur for the names of a few prominent professors under whom she could learn more about structural biology and biophysics. One name was Angela Gronenborn.

In 2006, Zorba netted another NMR-related internship in Japan. There, she asked her adviser for the names of prospective mentors. Again, Angela Gronenborn's name came up.

Gronenborn is Pitt's UPMC Rosalind Franklin Professor and inaugural chair of the Department of Structural Biology. Pitt recruited her from the National Institutes of Health in 2004 not only to lead the department, but also to play a major role in establishing the graduate program in molecular biophysics and structural biology.

"If you look at where medicine is going, biomedical science is less about describing phenomena than it is about looking at the more quantitative aspects of what's happening on the subcellular level," Gronenborn says. "We're using the methods of chemistry, physics, and math to look at biomedical problems in that way."

This approach, she says, means the next generation of treatments and potential cures can be tackled on the most fundamental level. While investigators may understand the "big picture" of many diseases, drilling down to the molecular level of illness and injury may provide new and better treatment targets, she says.

"When I came here for my interview, I found that she's not only a great scientist," Zorba says of Gronenborn, "but she has a great personality and a desire to help students. I also saw that Pitt has the latest equipment available in terms of NMR." (The 900 megahertz magnet that dwells in the basement of Biomedical Science Tower 3—known as BST3—is one of a handful of such devices in the United States.)

So the program director was great, as was the equipment, but why join a program in its first year?

"I was so impressed by the faculty who were recruited to this program," Zorba says. "I did think [the program] is very new, and sometimes it's risky to take that step, but I could see that [faculty] research was very exciting, that the faculty was very experienced and very approachable. And I loved the intimacy the department offered."

By "intimacy," Zorba says she means the deeply collaborative environment she found herself in from the moment she arrived on campus. She cites Thursday's lunchtime lectures as an example. Students, faculty, and postdocs from Pitt's structural and computational biology and chemistry departments, along with their counterparts at Carnegie Mellon University, assemble to hear a speaker over their midday meal.

"We can learn from the course of [the speaker's] career," Zorba says. "And [with the variety of investigators present], I think the lectures help all of us think about our problems on a larger scale."

Then there are the weekly lab meetings—the record setter went from 2:30 to 8:30 p.m.

"Our lab meetings are not traditional," Zorba says. "There are no PowerPoint presentations." Participants take turns critiquing one another's work, Zorba says, and students are fully vested in the process.

In the lab, Zorba has veteran structural biology colleagues to tap for information. And elsewhere in BST3, she has computational biologists, neuroscientists, and others who, she says, are always willing to help.

"Being in this building is like being at a conference. Everything is here, and it's up to you to take advantage of it, to exploit the opportunities," she says.

Zorba is attempting to determine the structure of a protein kinase (the aurora-A kinase) involved in promoting the growth of various cancers.

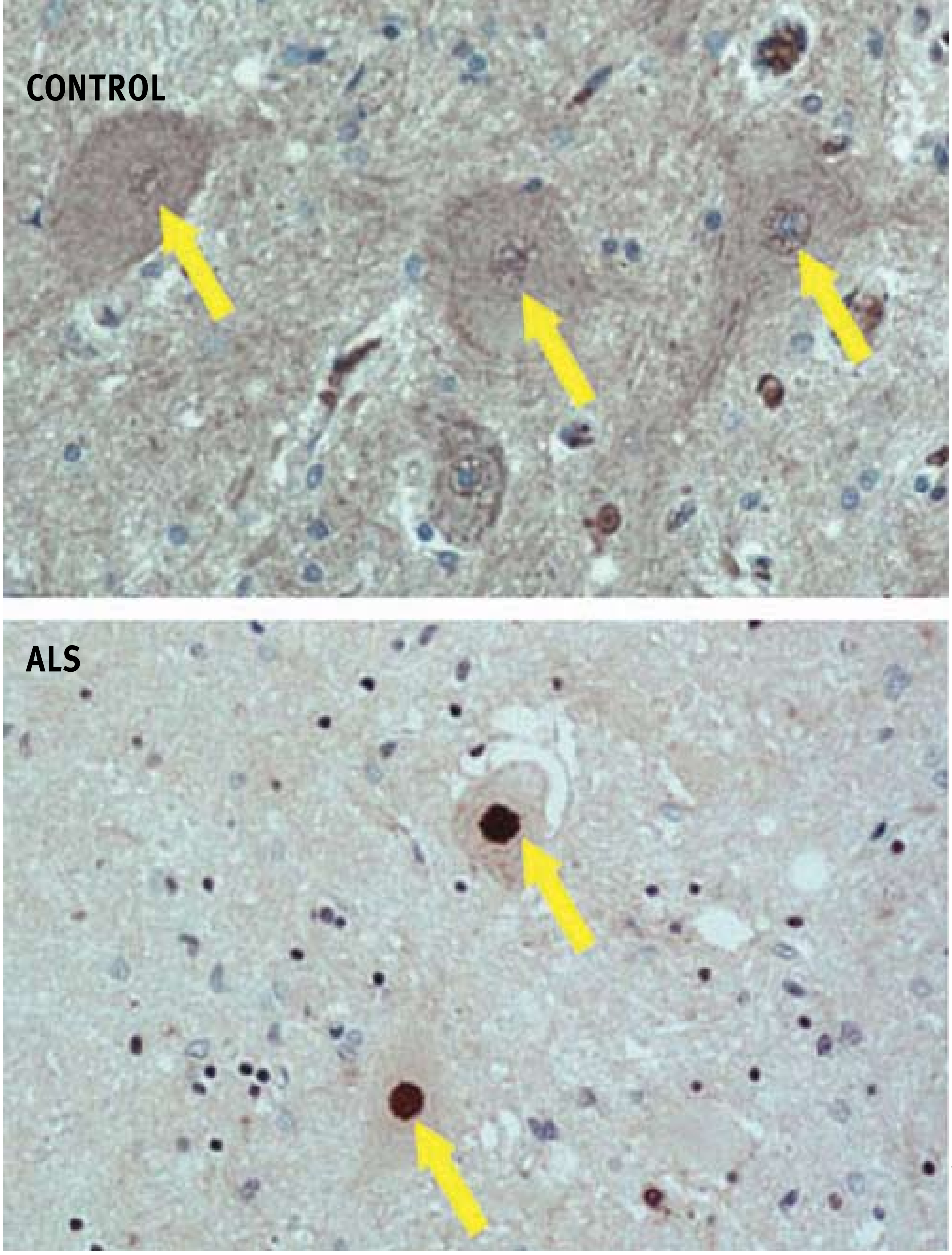
She says that if she is able to figure out what makes the kinase active, it might be possible to develop a drug to deactivate it or to at least inhibit its function, slowing cancer's spread.

As part of this process, she's trying to figure out the structure of a terminus on the kinase that has yet to be mapped. Zorba thinks the terminus functions "like an arm waving very, very rapidly." In doing so, she thinks, it blocks an anticancer drug from attaching to the kinase and doing its job.

She'd like to find a different protein that will bind to the end terminal, putting an end to its relentless waving and allowing the drug to connect with the kinase. Her approach is analogous to removing the goalie from a hockey game and allowing free shots at an open net.

NMR will help her map the domain of the terminus and conduct experiments with the other blocking proteins; the method captures proteins in action.

"It's exciting. The applications are there, and I think that NMR offers the best picture of what proteins look like in our bodies," Zorba says. "Right now it's as close to the truth as I can get."



R. BOWSER/ C. KOLARCIK

Kolarcik and her adviser, Robert Bowser, note that a certain protein (retinoic acid receptor beta) is present in the nuclei of motor neuron cells of ALS patients (bottom image) and control patients (top). The protein, however, is found in higher concentrations in the ALS group, leading the researchers to believe it plays a role in neuronal cell death.

Horn expects that Pitt's menu of grad school options will keep expanding. New ones, he says, will spring from the emergence of new ideas in science that can't be furthered by existing programs. This is one of those situations, he adds, in which progress is driven from the bottom up: One scientist with a novel way of doing things spreads the word to the greater community, others refine that idea, discoveries are made, and a discipline emerges.

Pitt, Horn says, will keep an eye on emerging fields of inquiry and, in the meantime, will strive to be a medical school that nurtures both ends of the bench-to-bedside path of medicine. ■