

THE DABBLER

Scientists sometimes hold pharmacology in little regard because they consider it a derivative of other fields. To Phil Cole that's its big appeal.

By Rebecca Skloot • Photo: Keith Weller

PHIL COLE IS A DABBLER. AT any given time, his lab buzzes with nine or 10 research projects that focus on enzymes, hormones and proteins. He works on everything from identifying molecular structures to creating potential drugs for AIDS or cancer. In some fields, dabblers are frowned upon, considered unfocused, but Cole, the 39-year-old E.K. Marshall and Thomas H. Maren Professor and director of the Department of Pharmacology and Molecular Sciences, is in the forefront of a field in which dabbling is the key to success.

People hear the word "pharmacology" and imagine a white-coated pharmacist filling prescriptions at the neighborhood pharmacy. But that's a far cry from Phil Cole, with his uniform of khakis and L.L. Bean pullovers. Cole divides his time between a small corner office where he works to build a department, and a modest lab, where he's trying to develop drugs. If you ask him what pharmacology is, he'll lower his eyebrows under his metal-rimmed glasses, wrinkle his brow and crane his head forward. His left hand will disappear into thick brown hair, he'll smile as if he's not quite sure himself, and say, "I think historically pharmacology has had something to do with the interface of chemistry, biology, medicine, and drugs—either the design of drugs, the effects of drugs on animals and people, or the identification of new drug targets."

But what pharmacology is today seems

to be up for negotiation, as a new generation of pharmacologists enters the scene. As always, the field represents a blending of sciences, but whereas that once required a biologist in need of a particular molecule for an experiment to ask a chemist colleague to create it, that's increasingly not necessary. Today's pharmacologists focus on the biology of a disease before producing drugs that target it. And so, there's a benefit in training researchers equally skilled in chemistry and biology.

And that, says Jeremy Berg, who in 1999 chaired the search committee for

tists alike. "When somebody's been at the top of their class in college, our M.D./Ph.D. program, in his residency and his postdoc, you have to admit, there's a pattern there," Berg says.

Some of the most exciting examples of Cole's biological awareness are evident in his work with protein kinases—a vast family of enzymes that regulate metabolism and cell growth. Protein kinases act much like thermostats that monitor cellular activity to make sure the body functions properly. Blood cells, for example, die and are replaced each day in a process

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Pharmacology's director, was just what Hopkins was looking for. "We were hoping to create a department where scientists are well informed about the biological questions and at the same time skilled in chemistry. To lead it we wanted someone who would know what's possible and how to get there." When Berg polled the Pharmacology faculty about what they wanted in a director, time and again the answer came back: "Somebody like Phil Cole."

Cole is trained in medicine and in basic science and has a foot in both worlds. A decade ago, as an M.D./Ph.D. student at Hopkins, he captured the respect of pharmacologists, chemists and clinical scien-

that's closely regulated by a protein kinase that kicks into action and tells the body to produce more cells. Once normal blood levels are restored, the protein kinase turns itself off. If, however, the protein kinase malfunctions and doesn't stop production, blood cells divide out of control. The result is chronic myelocytic leukemia (CML), and often death.

Several years ago, Cole and others realized that for diseases like CML, where kinases malfunction and stimulate production of cancerous cells, if they could create molecules that block protein kinases they would have a powerful tool for stopping cancer. Out of that idea, the mega pharmaceutical firm Novartis went



on to develop a protein kinase inhibitor whose results in clinical trials proved so dramatic that the FDA recently approved the drug in record time. Now, Cole is at work on developing other protein kinase inhibitors which he thinks may accomplish similar feats with other malignancies—breast cancer, for example—as well as autoimmune diseases. And unlike modern chemotherapy, these molecules only kill the cancer cells.

“Most chemotherapy consists basically of bludgeoning people with toxic compounds and hoping that the cancer dies before the patient does,” says Berg, professor and director of Biophysics and Biophysical

Chemistry. “With these inhibitors, there’s hope for something much more focused, rational and specific.”

But since Cole is a dabbler, he’s not limiting himself to work on protein kinases. “We block lots of things,” he says. “Protein kinases are just the beginning.” He also blocks, for instance, enzymes involved in gene regulation that may be important in treating cancer and HIV. And he blocks melatonin, the hormone that got him into pharmacology in the first place.

After Cole graduated from Hopkins’ M.D./Ph.D. program in 1991, he did a residency in medicine and endocrinology at Brigham & Women’s Hospital in

Boston, and there, began seeing patient after patient who complained about being tired all the time. The story was always the same: blood work and physical exam would show nothing wrong, yet these people were depressed, unable to stay awake, or even to carry out normal activities. Cole and others began thinking about melatonin, a hormone that regulates fertility and circadian rhythms and which is often implicated in such mood problems as seasonal affective disorder. Cole searched the literature on melatonin and realized that little was known about its effects on the body. To learn more, he decided to make a molecule that blocks melatonin—a melatonin inhibitor. With that step now complete, he’s busy studying circadian rhythms.

Recently Cole helped land a \$1.8 million grant from the William Keck Foundation that will go toward a center for rational design of biologically active molecules for the departments of Pharmacology, Biophysics and others. He now includes the Division of Clinical Pharmacology in his departmental faculty meetings and hopes to work closely with that group in setting up clinical trials as drugs are developed.

“Designing and participating in clinical trials is where the rubber meets the road in pharmacology,” Berg says. “It’s a real opportunity for doing both service and basic research.” Trials are the final product of years of dabbling by researchers in chemistry, biophysics, genetics and more. Cole’s two big dreams for his department, he says, are to keep building bridges among the sciences that make up pharmacology and to develop an abundance of new drugs.

“Believe it or not,” Cole points out, “pharmacology isn’t held in high esteem, even among scientists. ‘Researchers don’t usually say ‘I’m a pharmacologist.’ They say, ‘I’m a geneticist, I’m a molecular biologist, I’m a chemist.’ There could be a perception problem, because the field is a derivative of other fields. But to me that’s what’s wonderful about it. It’s so multidisciplinary.” ■