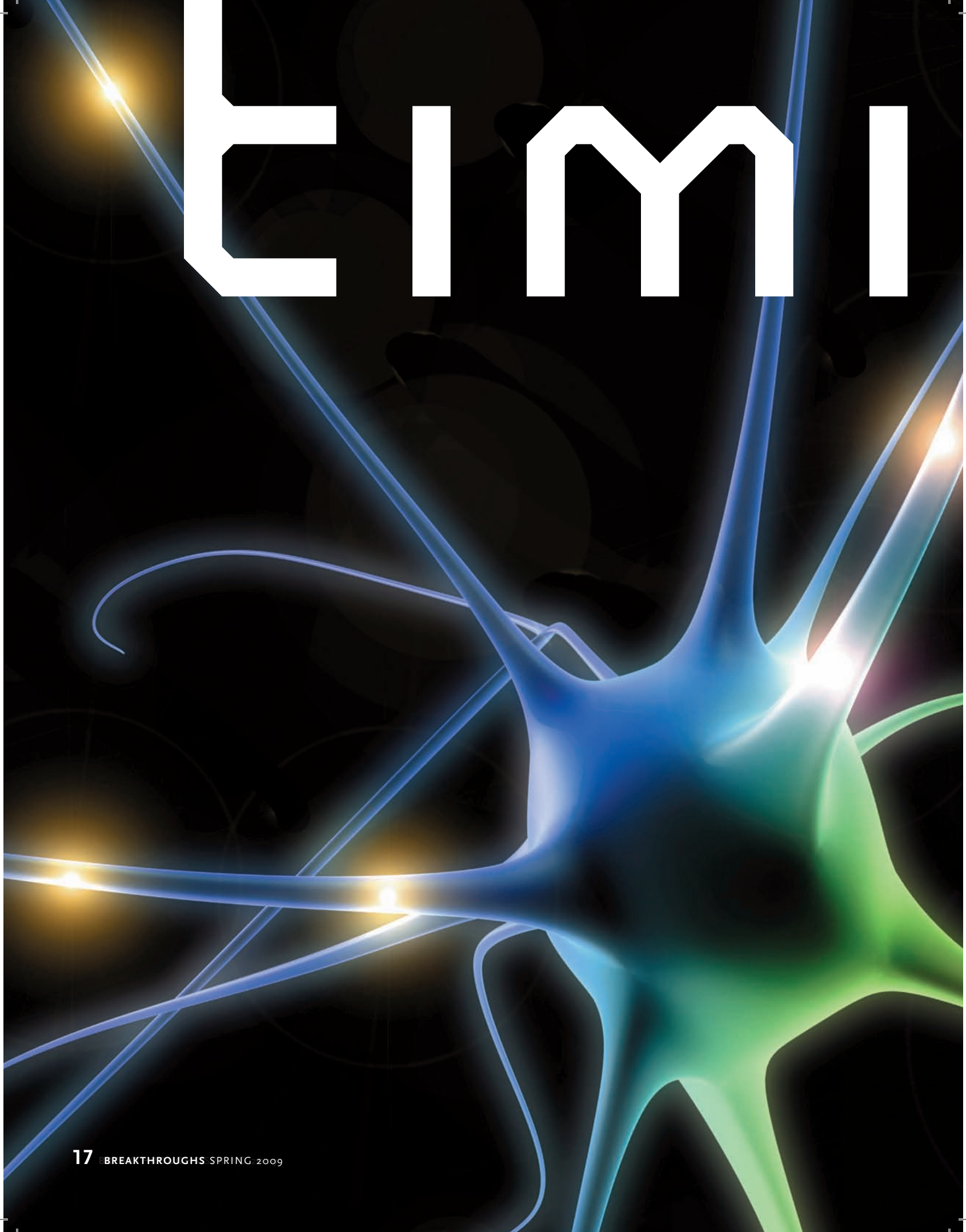


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NOG IS everything

by Kathleen M. Wong

There's a problem with the pace of new drug development: it's standing still. Fewer new medications have made it to pharmacy shelves in the last three years than at any time in the last 30. The pharmaceutical juggernaut that has helped revolutionize medical care and stock our medicine cabinets is beginning to grind to a halt.

By rights, drug development should be accelerating, not slowing down. Scientific understanding of how the body functions—the details of its metabolic pathways, protein structures, genetic controls, and biochemical reactions—has never been stronger. But **Dr. Marc Hellerstein** argues that most recently approved drugs were discovered in spite of, rather than because of, these advances. A Berkeley professor of nutritional science and toxicology, board-certified physician, and professor of medicine at UC San Francisco, Hellerstein says researchers have overestimated their knowledge of the component pieces of living systems, and are discovering, to their chagrin, that Mother Nature still has a few surprises up her sleeve.

Current drug development strategies involve screening vast libraries of biochemical compounds for molecules that interact at key points in a disease pathway. This approach, however, ignores a fundamental problem. "Biochemical networks are adaptive and organized to defend a certain pattern of molecular flow. When we think one thing will happen by intervening at a node, often something completely different happens downstream." In short, our fragmented understanding of how the body works isn't good enough for molecular target practice; living things are much more unpredictable than the sum of their pieces. Intervening in this manner can be compared to damming the headwaters of the Amazon River; it's unlikely to have a predictable effect at the river's mouth. The same goes for tampering with a molecule that is just one of many elements that affect blood sugar, body weight, or any other aspect of health.

a stopwatch for clinical studies

Hellerstein has focused many of his research efforts on developing more direct methods to evaluate health treatments. To do this, he has developed elegant and powerful techniques to observe the flow of key molecules through complex pathways in body tissues. Instead of determining how strongly a drug affects an isolated protein or gene, his method actually observes the dynamic turnover of molecules and cells. This allows him to track measures that explicitly drive or modify disease processes—such as the growth of cancer cells, the movement of cholesterol in the body, and the lifespan of immune cells.

To do this, Hellerstein enlists molecules already found in the body, such as cholesterol, glucose, or water, to act as cellular markers. But his molecular versions are slightly different, each carrying an extra neutron in their atomic structures. To the body, these tracer molecules are indistinguishable from their natural counterparts. They are broken down, incorporated into tissues, transported, and eliminated normally during metabolism. But because they are slightly heavier than their naturally occurring counterparts, the tracers are easy to identify in the laboratory with a mass spectrometer.

Administering a tracer to a patient marks the click of a virtual timer button. Any cells containing the marker at a later



Under mass spectrometry, Hellerstein's tracers become a "molecular stopwatch."

date must have acquired the tracer after the initial administration. The tracer thus introduces the element of time to a study. Health interventions such as drug administration, dietary shifts, or exercise started at this point can be evaluated by analyzing molecules and cells containing the tracer. The pattern or amount of label in strategically targeted molecules is then analyzed by mass spectrometry, and mathematical tools are applied to calculate flow rates into and out of the pathway. In this way,

Hellerstein shines a light into what has largely been a black box—the dynamic performance of complex biological systems.

Hellerstein's approach is appropriate for a vast range of physiological applications. With certain tracers, such as heavy water, Hellerstein says, "you can measure literally anything—all the proteins synthesized in the body, the number of new cancer cells the body is producing, and much more." Best of all, the technique measures the effects of interventions on the tissues of fully assembled living organisms, rather than their impacts on isolated components of metabolic pathways. "Full living systems have very different properties and behaviors than their components alone. The results are also more relevant to health in the end," Hellerstein says.

Researchers are already using the technique to study areas that span the entire range of human health. For example, Hellerstein has adapted his assay approach to mark the birth of new brain cells.

Scientists developing drugs for depression, Alzheimer's disease, traumatic brain injury, and other diseases that involve neurogenesis now routinely use Hellerstein's assay to evaluate their products. Hellerstein himself has already identified one drug that encourages brain cell production: Lipitor, a widely used cholesterol inhibitor.

a prognosis for cancer

The power to observe changes in health over time makes Hellerstein's tests ideal for obtaining a prognosis for different types of cancers. Because a given type of cancer can be triggered by changes in several different genes, each case must be evaluated individually to determine the right course of treatment. Hellerstein is developing tests that will help doctors distinguish which patients need intensive treatment and which will do fine with either milder therapy or no interventions at all.

One such disease is prostate cancer. The condition principally affects older men, who often live with the disease long enough to die from other causes. But the faster the tumor cells in the prostate grow, the worse the man's prognosis is likely to be. The current diagnostic method is to examine levels of a blood protein that increases in proportion to the size of the prostate, and then to perform a needle biopsy. Neither method measures the growth of cancerous cells over time. This scenario leaves doctors facing a dilemma: an untreated case of aggressive cancer could potentially be fatal, but treating everyone by removing the prostate and providing chemotherapy isn't a good option either. The side effects of such treatment—urinary incontinence and impotence—can be worse than living with milder cases of the disease. "The first rule of medicine is *primo non nocere*: first do no harm. You don't want to treat people with toxic cancer drugs if they aren't going to have a problem. But those people you don't treat might end up dying," Hellerstein says.

Hellerstein has devised a much less invasive diagnostic that is now being tested in clinical trials. Patients are given heavy water to drink and samples of their ejaculate are examined for the tracer. "We find that the prostate cells in seminal fluid accurately represent the types of cells being turned over in the gland. The prevalence of labeled cells appears to tell us how aggressively the tumor is behaving," Hellerstein says. "It's a very attractive diagnostic compared to a needle biopsy, which can be painful."

Hellerstein is using a similar approach to predict the course of another unpredictable disease, chronic lymphocytic leukemia. Still being tested in clinical trials, the method points to a strong correlation between the rate of cancerous cells being produced and the aggressiveness of the most common form of blood cancer.

This time-sensitive method is ideally suited to study problems with a wide variety of root causes. For example, how are metabolic changes affected by diet, exercise, temperature, and other factors? Scientists have long puzzled over this, and debated the length of time that fat cells persist in the body. When Hellerstein gave


healthy human subjects heavy water to drink, he found that new fat cells containing heavy water survived for no longer than six months, disproving the classic dieter's mantra, "a moment on the lips means forever on the hips." Scientists are using this same approach to examine the rate of fat cell production and metabolism. For example, scientists aren't certain why mice lacking certain fat metabolism genes don't get roly-poly even when fed a high-fat diet. By tracking the accumulation and disappearance of fat cells and their main lipid components, Hellerstein's assay can pinpoint whether these mice can't make fat, can't store fat, or whether some other aspect of the pathway has been disrupted.

better shots for all

A more venerable area benefiting from rate-tracking studies is the realm of vaccines. Immunizations are considered the single most cost-effective public health measure in history. Even so, after 200 years of use, scientists still don't have a detailed understanding of how they work. It is known that adding small amounts of antigen to the body can raise an infection-busting immune response, and that white blood cells programmed against the antigen may persist for decades. But whether immunity is maintained by clones of cells sensitized immediately after immunization, or naive cells that continually encounter hidden pockets of antigen, remains a mystery. "Does the immune system have a true long-term memory or is it really a short-term memory with frequent reminders? Nobody knows," Hellerstein says.

Hellerstein is now collaborating with researchers at UC San Francisco and Emory University to determine whether vaccines give rise to long-lived immune cells or continually stimulate the production of new lymphocytes. The answers aren't merely academic. They have tremendous implications for developing new vaccine ingredients and strategies that will ultimately help scientists design longer lasting, more effective immunizations. This knowledge could be used to help patients with lupus, multiple sclerosis, and other autoimmune diseases.

Hellerstein's immunological research has already dispelled earlier notions about the effect of HIV on T cell counts in AIDS patients. At first, researchers believed that HIV was directly responsible for killing these key elements of the immune system. By tracking the birth and demise of T cells, Hellerstein has helped demonstrate that deficiencies in the production of new T cells is just as integral to the disease as their destruction.

Hellerstein's expertise with molecular tracers is now much in demand. "I frequently get calls from people around the country who've read a paper and say, 'How'd you like to be on my grant?' The same is true for drug companies, who would like to understand what their drug candidates are doing. So we are constantly collaborating with other researchers." As Hellerstein himself might say, it's about time for this kind of change. 



THE Doctor IS IN

The doctor is in at Berkeley's Nutritional Science and Toxicology Department. Of the department's 22 faculty and adjunct faculty, no fewer than four are M.D.–Ph.D.s, and their interdisciplinary training brings a uniquely broad and valuable perspective to Berkeley research.

This range of expertise is shared by only a small handful of other Berkeley professors.

"An M.D.–Ph.D. can see problems from both the clinical and basic research sides, and marry both of them in their research programs," says **Joseph Napoli**, Chair of the Nutritional Science and Toxicology Department.

Like other department faculty, professors **Chris Vulpe** and **Marc Hellerstein** and adjunct professors **Ronald Krauss** and **Dale Leitman** study metabolic biology, which examines the impact of diet and nutrition on health and metabolism. Their medical experience qualifies them to set up clinical trials, overseeing every step of the path from lab bench to bedside.

The presence of so many M.D.–Ph.D.s makes the college a particularly good resource for students interested in the health professions. "If you really want to know what it's like going to medical school, how you have to prepare, or what life afterwards is like, talk to these people. They know—they have the real-life experience," Napoli says. —KW