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| **The Geneticist & the Biochemist**  **By Tim Stephens**  **How a friendly rivalry illustrates the two cornerstones of biomedical research**   |  |  | | --- | --- | | Sullivan Photo: Jim MacKenzie | Kellogg Photo: Jim MacKenzie |   The billions upon billions of cells that make up a human being all descend from a single cell, the fertilized egg. Cells are the basic building blocks of life, and even cells from different organisms share common features and a common evolutionary origin. In fact, the genes involved in basic cellular functions have remained largely the same over billions of years of evolution. That's why scientists trying to understand how human cells work study such unlikely creatures as flies, worms, and yeast—"model organisms" that yield valuable insights into human biology and diseases.  Researchers in UCSC's Department of Molecular, Cell, and Developmental Biology (MCD biology) use model organisms to study, among other things, the molecular roots of cancer. Geneticist William Sullivan (above left) and biochemist Douglas Kellogg (above right), for example, both study the regulatory mechanisms whose failure turns normal cells into cancer cells.  But the two UCSC scientists approach biomedical research from different angles, and over the years they have maintained a friendly rivalry over whose approach is more fruitful. As a geneticist, Sullivan is particularly interested in the genes that are responsible for regulating cell growth and division. The genes carry instructions for making specific protein molecules, and Kellogg, the biochemist, focuses on those proteins and how they carry out their regulatory functions in the cell.  The two researchers began debating the relative merits of genetics and biochemistry years ago, when Sullivan was a postdoctoral fellow and Kellogg was a graduate student working in the same laboratory at UC San Francisco. Their sparring lives on in a tongue-in-cheek parable Sullivan published in the 1990s, which Kellogg countered with his own version. The stories have been widely reprinted and posted on numerous academic web sites (see [bio-debate.html](http://review.ucsc.edu/spring04/bio-debate.html)). Sullivan has even been asked to autograph students' copies of his essay when visiting other universities.  The popularity of the stories is partly due to their humor, but they are also useful teaching tools for explaining these two fundamental approaches to basic research in biology.  "Maybe I should do more of that—it only took me an hour to write that, and it takes me two years to produce a scientific paper," Sullivan quips.  The fictional protagonists of both stories are a retired geneticist and a retired biochemist, who live on a hill overlooking an auto factory. Having spent their lives in pursuit of higher learning, the two characters are wholly unfamiliar with how cars work. So they set about studying them in their accustomed ways.  The biochemist gets himself a car and immediately starts taking it apart and studying its component parts. The geneticist, meanwhile, strolls down the hill and ties the hands of one of the workers headed into the factory. While the biochemist gets covered in grease and oil, the geneticist watches the cars rolling off the assembly line and observes that they are all missing a certain part (the steering wheel) and fail to make the first turn in the road.  The analogy in the parable isn't perfect, but you can think of the factory workers as genes and the car parts they are responsible for as proteins and other cellular components. Geneticists knock out genes and study what goes awry in the resulting mutants. Biochemists isolate proteins and other molecules from cells and study their structures and interactions.  "I think one reason the stories struck a chord with people is that—in those days, at least—geneticists had the reputation of being armchair scientists and kind of arrogant, while the biochemists did all the nitty-gritty work," Sullivan says. "What I like about genetics, though, is that the experiments can sound ridiculous, yet they'll lead to the discovery of a major disease gene."  Kellogg acknowledges the power of genetics, but says biochemistry gets closer to the action. "Genetics gives you great tools for identifying a gene involved in a certain pathway," he says. "But genetics doesn't tell you what the gene does, so you also need the biochemistry to figure out what the protein produced by that gene actually does."  Not surprisingly, the two versions of the parable reflect the prejudices of their respective authors. In Sullivan's story, the geneticist's approach is successful while the biochemist flounders—an outcome that is reversed in Kellogg's version.  Today, a decade after their parables were first published, both Kellogg and Sullivan actually find themselves using a combination of genetics and biochemistry in their research. Instead of competing, the two fields have become the complementary cornerstones of modern biomedical research. And new laboratory techniques, based on advances in both fields, are giving scientists an increasingly complex and detailed view of the molecular interactions that make cells tick.  All cells pass through a well-defined series of steps, known as the cell cycle, as they grow to a certain size, copy their chromosomes, and divide into two new cells. Sullivan studies the regulation of the cell cycle in the fruit fly, a mainstay of genetics research for more than 100 years. Kellogg investigates the cell cycle using another classic model organism, yeast.   |  |  | | --- | --- | | DNAtubulin2.rezzed Photo: Uyen Tram | fin_cyto2_rgb_T_cover2 Photo: Anne Royou | | Combining genetics and biochemistry, Sullivan studies the effects of mutations on the cell cycle using staining techniques that tag different molecules involved in cell division with fluorescent labels. In the dividing wasp cells on the left, DNA is red and the protein tubulin is green. In the dividing fruit fly cells on the right, DNA is blue, tubulin is red, and the protein myosin is green (to see the Sullivan lab's movies of cells dividing, go to[www.biology.ucsc.edu/people/sullivan/images.html](http://www.biology.ucsc.edu/people/sullivan/images.html)). | |   Both Kellogg and Sullivan have identified gene mutations that disrupt normal cell growth and division. They are particularly interested in "checkpoints" in the cell cycle—points where the cell, in effect, makes an assessment and decides whether to proceed to the next part of the cycle. Disruption of the checkpoint mechanisms is one of the hallmarks of cancer cells.  Kellogg's biochemical investigations in yeast cells are helping to sort out the interactions between different proteins involved in checkpoint mechanisms. He compares their dynamic interactions to a constantly running engine that is highly responsive to signals coming in from other parts of the cell.  "It's really a remarkable system, and we're just scratching the surface," Kellogg says. "We have these little stick-figure diagrams for something that is far more sophisticated and complex than a car engine."  Tremendous progress has been made over the past ten years in understanding how the cell cycle is controlled. Cell-cycle checkpoints have become a major focus of efforts to develop new cancer drugs. Nevertheless, the clinical payoff so far has been disappointing, according to Sullivan.  "We have learned so much about what drives the cell cycle, and amazingly it has had almost no impact on what doctors currently do to treat cancer patients," he says.  So Sullivan has joined the growing effort to translate advances in molecular biology into the arena of cancer therapy. His lab has developed a system for evaluating the effectiveness of cancer drugs against cells that have specific mutations in known cancer genes.  Traditionally, the drugs selected to treat a particular type of cancer have been chosen on the basis of the tissue in which the cancer originated. So studies are done to find the drugs that most effectively kill, say, lung cancer cells. But lung cancer can result from defects in many different genes that control the cell cycle.  "One person's lung cancer cells are not the same as another person's," Sullivan says. "Doctors would like to be able to define each individual's cancer genetically and then say: These are the drugs that will be effective against cancer cells with these particular genetic mutations."  In general, basic research in biology does not lead directly to new medical treatments. Rather, it provides the fundamental knowledge that enables medical researchers to understand and combat diseases.  "The work we do to understand how a gene or protein works in a model organism can be used by people in the clinical setting to accelerate their understanding of human diseases," says John Tamkun, professor and chair of UCSC's Department of MCD Biology.  Tamkun, for example, studies genes and proteins that control which other genes in a cell are turned on. Some of the genes studied in his laboratory have turned out to be mutated in certain human cancers.  Other members of the department are investigating the genes and proteins that control the growth of nerve cells and the formation of connections between neurons in the developing nervous system. Their work has implications for understanding neurological disorders and treating injuries to nerves.  Harry Noller, Sinsheimer Professor of Molecular Biology, has earned international acclaim for his groundbreaking work on the structure of ribosomes, the protein factories of all cells. The ribosome is a complex molecular machine one millionth of an inch in diameter. Inside every cell, tens of thousands of ribosomes take orders from genes and turn out fresh proteins with amazing speed and precision.  Noller's findings have practical significance because many antibiotics work by binding to and disrupting bacterial ribosomes. Understanding how the ribosome works will help pharmaceutical companies develop new and more effective antibiotics.  The identification and characterization of potential "drug targets" is an increasingly important outcome of research in molecular biology. Molecules that play important roles in the cell are of great interest to pharmaceutical companies, because a drug that blocks or enhances the target molecule's activity is likely to have therapeutic value.  Just about everything scientists do to unravel the molecular mechanisms of cellular processes is of potential value to the pharmaceutical industry, says Manuel Ares, a professor of MCD biology.  Ares, Noller, and others in the Department of MCD Biology are contributing to a great flood of new information and insights that is making this area of biology one of the most dynamic disciplines in science. The field, in fact, is changing so fast that introductory textbooks in cell biology become outdated within a year or two of their publication.  "The area of biology that our department covers evolves so rapidly that even our undergraduate curriculum is being revised constantly," Tamkun says. "For students, that really highlights the value of being at a research university where the faculty are actively engaged in these areas."  One factor behind the increasing pace of discovery in biology is the use of new "high-throughput" technologies. For example, DNA microarrays (or "gene chips") are enabling scientists to monitor the activity of thousands of genes at once, rather than studying one gene at a time.  "You can look at 10,000 or 15,000 genes in a single experiment, and it's saving years of work," Tamkun says.  Ares has established a microarray facility at UCSC and is developing special microarrays for detecting differences in the way cells interpret the information in their genes. His research is revealing a whole new level of complexity in gene regulation. |