Big Plans for Small Molecules: NIH Launches Chemical Genomics Initiative

The National Institutes of Health, as part of its new “Roadmap for Medical Research,” is launching a major chemical genomics initiative. Directors of almost every institute within NIH gathered in late September to announce plans for the Roadmap, a special program to speed the transition of basic research to medical advances (see box p. 1741). Little attention was given to the chemical genomics initiative, spearheaded by the National Human Genome Research Institute (NHGRI), but it represents a major commitment to a new approach to public sector drug discovery.

Chemical genomics is “the broad-based use of small molecule, drug-like compounds to study the biological function and therapeutic potential of the genome,” in the words of Chris Austin, M.D., senior adviser to NHGRI director Francis Collins, M.D., Ph.D. (Collins, in papers, lectures, and interviews, has been promoting chemical genomics since the April completion of the human genome sequence.) Chemical genomics is a departure from the way functional genomics typically is addressed outside of industry. The vast majority of academic biologists use genetic approaches, including knockout mice, dominant negative mutants, and, more recently, RNA interference, to figure out what genes do. Small molecules are gaining ground, but only slowly.

Why, until now, have small molecules been largely ignored? Compound libraries and screening robots are expensive, but a bigger barrier is “the religious belief that, ‘No, that’s not what I do, that’s what someone else does,’” said pharmacologist John Lazo, Ph.D., of the University of Pittsburgh. Until recently, Lazo said, “screening a compound library was considered, you know, just slightly above garbage picking.” Lazo said he is enthusiastic about the new initiative. “This is a really wonderful resource that, from my vantage point, will have as much power as what the revolution in molecular biology and genetics has done for biology.”

That optimism reflects the fact that only a miniscule number of possible small molecules have ever been synthesized, much less tested for effect. The NIH will build an initial library of 500,000 compounds and will create and equip one or more screening centers. Academic researchers will create the assays used in the screens. “The kind of capital and resources that are required to do this kind of screening are very large, so you want to centralize that,” said Austin. “The model is exactly the same as how the genome project was done.”

Two very different kinds of screens will take place. Functional screening involves testing compounds against a known target, for example the Cox-2 enzyme, and assaying for inhibition. Sometimes called “reverse genetics” or “reverse pharmacology,” it is what the pharmaceutical industry routinely does to discover new drugs. The other approach is phenotypic screening, the unbiased testing of compounds in cells without knowing their targets, and assaying for varying effects—for example, cell cycle arrest—which could identify potential anticancer compounds. This “forward genetics” approach was once favored by the drug industry, but fell out of favor once genetic engineering made large quantities of purified proteins available for target assays in the 1970s. “You need both types of approaches—they complement one another,” said Lazo. “To do one at the exclusion of the other would be foolish.”

The NIH has big plans for phenotypic screening. “Unlike the pharmaceutical industry, which takes Cox-2 and only Cox-2, and then hits it over the head with 500,000 different compounds, we’re targeting a cellular process,” said Craig Crews, Ph.D., of Yale University, New Haven, Conn., one of a handful of academics already doing phenotypic screening. Because no assumptions are made, results are unpredictable: A given compound could halt cell growth or speed it up, set off signaling cascades, change the cell’s structure in new ways, propagate it, or kill it. “No matter which way the results are, they’re informative,” said Crews, “as opposed to yes–no.”

In 1999, Harvard chemist Stuart Schreiber, Ph.D., used a phenotypic screen to identify a novel drug target, Eg5, that is crucial for spindle formation in mitotic cells. As the first such non-tubulin target discovered, it would never have occurred to researchers to deliberately look for such a “mitotic spindle bipolarity protein,” but Eg5 emerged in a phenotypic screen. Cytokinetics, a South San Francisco biotechnology company, now has an Eg5 inhibitor in phase I clinical trials for cancer.

The hope is that phenotypic screening will deliver many such unexpected drug targets. The NIH expects to go beyond the targets favored by the pharmaceutical industry: enzymes, G protein-coupled receptors, ion channels, and nuclear hormone receptors. “The definition of a drug is going to be changing,” said Crews. “The Holy Grail [is] compounds that can disrupt protein–protein interactions.”

Whether many such drugs can be found has been questioned. Pfizer scientists Andrew Hopkins, Ph.D., and Colin Groom, Ph.D., last year argued in Nature Reviews Drug Discovery that only 10% of the human genome is “druggable,” with perhaps only half of those targets likely to have utility in...
treat disease. The NIH is betting that the number is far larger. “We won’t know until we go out there and do it and find out,” said Austin. “We have the luxury, and, one could argue, the obligation in the government setting to question those assumptions.”

Limited druggability “is an easy argument to make,” agreed Lazo. “But I think that until you do the experiment, you really don’t know the answer.” The naysayers, said Lazo, “are the same people who said you’ll never be able to make a Gleevec.”

Screening efficiency is another issue. The biggest problem in pheno-typic screening is figuring out what proteins the small molecules are hitting. That is necessary for developing actual drugs because small molecule probes themselves rarely have drug-like qualities such as a long plasma half-life, the ability to be absorbed into the bloodstream intact and to reach target cells, minimal toxicity, and good oral bioavailability. Screening “may very well generate a lot of very interesting biological activities, but then the bottleneck will be target identification and follow-up,” said Steve Adams, Ph.D., chief scientific officer of NeoGenesis, a Cambridge, Mass., biotechnology company.

Austin said that the NHGRI will develop large-scale target-identification methods to break this bottleneck. But he stressed that the NIH is not getting into the drug development business. “The NIH’s main purpose … should not be to do what the pharmaceutical industries are doing already,” he said. Aside from target discovery and validation, and some early medicinal chemistry and lead compound optimization, drug development will be left to the drug industry, with the possible exception of drugs for certain orphan diseases.

Other sticky issues remain unresolved. The NIH is philosophically committed to entering all results in a publicly accessible database, as was done with the human genome sequence. But it may delay such disclosure to allow researchers exclusive use of screening results for their own assays, some of which they have spent years developing. “We don’t want to kill the goose that lays the golden egg,” said Austin. “If our release requirements are so stringent that people don’t come to us with assays, then we’ve vitiated the purpose of having the screening facility in the first place.”

Intellectual property poses another dilemma. Some degree of exclusivity seems necessary to ensure commercial development of promising compounds, and the NIH may patent some of them. But it will have to be careful not to set too many conditions on licensees, said Adams. “The pharma industry needs, indeed insists, on being able to have control over the development and commercialization process,” he said. Few relish the prospect of more protracted legal disputes like those surrounding AZT and Taxol, two drugs developed at the NIH and licensed to industry. The NIH, said Austin, will consult with industry before setting any policies.

Despite the uncertainties, the NHGRI is gambling that chemical genomics will pay off in new kinds of drugs. The stakes are high, although the exact cost of the initiative has not yet been calculated. The expense “will be considerable,” said Austin. “What we’re talking about is not cheap.” But, like its genome project antecedent, it is a leap into the unknown, with unpredictable benefits. “We haven’t even begun to explore chemical space,” said Lazo. “It dwarfs the human genome.”

—Ken Garber