DOE to Map Expressed Genes

The Department of Energy is launching a new effort to map and partially sequence all the expressed genes, or complementary DNAs, in the human genome. It's not a radical departure but rather a reorientation of the chromosome mapping effort that DOE is conducting as part of the Human Genome Project. The move is intended to "get the most useful biological information out early in the game," says David Galas, associate director of the Office of Health and Environmental Research, who oversees DOE's genome activities.

The development of a cDNA map has long been advocated by Victor McKusick, a geneticist and gene mapper at Johns Hopkins University. As McKusick says, cDNAs are "where the action is." They are DNA clones made from messenger RNA and thus represent only the transcribed, or expressed genes—they are pure content. For that reason, geneticist Sydney Brenner has already made cDNA mapping and sequencing the cornerstone of the U.K. Medical Research Council's genome effort. Says Brenner: If 98% of the genome is composed of junk, or noncoding regions, "the best strategy is to find the important 2% and sequence it first."

DOE is proposing to scour clone collections, or "libraries," to find all the cDNAs and then sequence a small stretch of each one, about 200 to 500 base pairs, to create a special type of marker known as a sequence-tagged site, or STS (*Science,* 29 September 1989, p. 1438). Once the sequence tag is stored in a database, any researcher can quickly "recreate" that piece of DNA by using polymerase chain reaction techniques.

The biggest technical obstacle is finding a complete set of cDNAs. The problem is that genes are expressed at different levels in different cells or tissues. Thus, a cDNA library made from, say, liver cells might contain 10,000 copies of one gene but just one or two copies of another. Pulling out the genes that are expressed at low levels has proved tough in the past, but several ingenious strategies are in the works.

DOE expects to support efforts to improve cDNA libraries and to sequence the expressed genes outside the national labs. Some of that work is already under way; for example, Craig Venter at NIH recently embarked on a 3-year project to sequence a short stretch of each of the 30,000 cDNAs expressed in the human brain. As the cDNA markers are generated, they will then be turned over to the national labs—and to the mapping community—where they will be positioned along the human chromosomes. This will instantly pinpoint the location of all the genes. So far, only about 2,000 of the 50,000 to 100,000 human genes have been mapped by any technique, notes McKusick.

True, the map location won't reveal the function of these genes, McKusick says, "but even having an anonymous gene in your hand is useful." For disease gene hunters—for example, those investigators looking for the Huntington's gene on the short arm of chromosome 4—the map will provide a host of new candidate genes. And further down the line, the mapped cDNAs will provide an ideal starting point for sequencing, say both Galas and McKusick. One of the chief criticisms of the genome project has been that sequencing in "no man's land"—the vast stretches of DNA of unknown function—will yield little useful information for an exorbitant cost. But no one quibbles with starting with genes, which are inherently interesting.

■ LESLIE ROBERTS

A Stirring Tale of Crystal Growth

When Dilip Kondepudi checked the batch of crystals under polarized light, he couldn't believe his eyes. Normally, the hundreds of crystals in the Petri dish would be evenly divided between right-handed and left-handed, but this time every last one was right-handed. It was like tossing a handful of quarters in the air and having every one turn up heads. "At first I thought it was contamination," he says, "but I checked." With each new batch, he found that all or almost all of the crystals had the same handedness, although it was even odds whether any given batch would turn up right- or left-handed.

In this way Kondepudi, a chemist at Wake Forest University in Winston-Salem, North Carolina, found a totally unexpected phenomenon—how the simple act of stirring a solution could guarantee that all the crystals in a batch would take on the same handedness. In retrospect, he says, the most surprising thing may be that no one had uncovered it before since the experiment is simple enough to do in a high school chemistry lab. But the details of the experiment, reported on page 975, may provide some useful insights into the long-standing question of how most of the molecules of life, including DNA, RNA, and proteins, came to exist preferentially in a right-handed or left-handed form.

It was in a quest for such insights that Kondepudi stumbled across his discovery. To understand how handedness can appear spontaneously, Kondepudi chose to study the crystallization of sodium chlorate. The individual molecules of sodium chlorate are symmetric, but when they crystallize they align themselves into either a right-handed or a left-handed structure. (This "symmetry breaking" does not occur in the formation of most of the well-known chiral—or handed—crystals, such as crystallized proteins, because in those cases the molecules themselves already have an intrinsic handedness.)

If a sodium chlorate solution is left undisturbed, hundreds of crystals will slowly form as the liquid evaporates. Examine these crystals under polarized light and you find that about half are right-handed and half left-handed. While studying this system, Kondepudi decided to stir it to keep thin multi-crystalline sheets from forming across its surface, and the results astounded him. Stirring the solution had somehow forced it to make crystals of only one handedness.

"The striking implication is that every crystal in a sample comes from one initial crystal," says Michael McBride, a chemist at Yale University who had to repeat Kondepudi's experiment himself before he could quite believe it. As Kondepudi explains it, two factors are at work: autocatalysis and competition. Once one crystal forms spontaneously, it catalyses the formation of many secondary crystals of the same handedness. But at the same time, something must be suppressing the formation of other primary crystals, and Kondepudi says it is "competition" for sodium chlorate molecules. The stirring greatly increases the speed at which secondary crystals form from the first seed crystal, Kondepudi says, so that "in just a few minutes the concentration [of sodium chlorate] drops rapidly." By contrast, in an unstirred solution it takes "10 hours or so" to get the same drop in concentration. With a lower concentration of sodium chlorate, crystals no longer form spontaneously but the existing crystals continue to grow. The result is that once one crystal forms spontaneously, it chokes off other spontaneous formations so that all the crystals in the solution are descended from the first one.

"This is the first simple system that has both autocatalysis and competition," Kondepudi says. Since these two factors are thought to explain how the molecules of life originally settled on one handedness, the stirred solution may give insight into much more complicated biological systems. Moral: In chemistry, as in life, stirring things up can be a good way to get results. ■ ROBERT POOL