GENETICS

Merck Gives Researchers Knockout Deal

Researchers struggling to figure out what newly discovered genes do in the body are about to get some help. The Merck Genome Research Institute announced last week that it is giving Lexicon Genetics Inc.—a biotech firm based in The Woodlands, Texas—$8 million to create 150 new strains of "knockout" mice, using a new technology the company has developed. Such animals, in which specific genes have been inactivated, are widely used to study gene function (see, for example, pp. 531 and 534). But what's winning plaudits for Lexicon and the Merck institute—a nonprofit foundation set up by the giant drug company—is a promise to make these mice available to academic researchers at nominal cost, no strings attached.

"I think [the program] is an excellent idea," enthuses endocrinologist Joseph Majzoub of Children's Hospital in Boston. "Many labs have the expertise that would allow them to exploit knockout mice, but the main hurdle has been the cost."

Currently, it takes up to 10 months—and as much as $100,000—to develop a knockout mouse strain. As a result, only about 1000 knockouts now exist. Lexicon's solution is to create a bank of genetically altered mouse cells that can quickly be used to develop knockout strains.

Company scientists first transfer a small bit of DNA into embryonic stem cells. This DNA will insert randomly into the DNA of the cells, disrupting any gene it happens to hit. The inserted DNA both knocks out the gene and, along with some of adjacent transcribed mouse DNA, becomes a unique sequence tag. "We can retrieve the sequence tag so we can know [the gene's] identity," explains Arthur Sands, Lexicon's president. Such tagging and retrieval improve upon current gene-trapping techniques, which are inefficient and work only with specific, active gene targets; Lexicon's technology—the details of which are proprietary—works on all genes.

During the next 3 years, Lexicon will put high-throughput robots to work generating 500,000 mutant mouse embryonic stem-cell clones—enough to tag each gene "an average of five times," says Sands. The cloned cells will then be frozen in liquid nitrogen. Sands expects to have 50,000 clones in the freezer by the end of this year.

Anyone with a new gene sequence could then pay to have Lexicon search through its computerized database of sequence tags—called OmniBank—to find any clones that have an insert in that gene. Cells from those clones can then be thawed and used to create the appropriate knockout mouse strains, a procedure that should take just 4 to 6 months rather than the usual 6 to 10, says Sands.

But in addition, the Merck institute is pulling together a committee of six prominent biologists who will select 150 clones for development into mouse strains over the next few years. Most of this first batch will involve genes known to affect behavior or the central nervous system, or which have been linked to complex diseases such as cancer or diabetes. With Merck support, Lexicon will generate 20 breeding pairs of each selected mouse strain, then turn those pairs over to a yet-to-be-named, nonprofit organization that will raise the mice and distribute them.

"Just 150 strains seems like a small number," says Majzoub, although he adds that it's a step in the right direction. However, even if the Merck institute provides just these strains, Lexicon's costs to academic researchers to obtain clones or mice directly should still be reasonable, Lexicon co-founder Allan Bradley of Baylor College of Medicine in Houston insists. "It will be priced so [academic] people can afford it," he notes.

–Elizabeth Pennisi

PLASMA PHYSICS

Report Says ITER Ignition Not Assured

Sustaining support for multibillion-dollar international science projects requires a fine sense of balance. Promise too much, and you risk a backlash when reality fails to meet expectations. Promise too little, and politicians may lose interest in the project. Last week, the $10 billion International Thermonuclear Experimental Reactor (ITER) shifted balance from the first to the second side of the political tightrope after a team of U.S. physicists and engineers concluded that scientists have been overly optimistic about the chances of achieving a self-sustaining burn.

The latest review comes at a critical time for the ITER program, which is preparing for negotiations later this year among Europe, Japan, Russia, and the United States on whether to spend the next decade building the massive machine (*Science*, 31 January, p. 612). Last fall, the U.S. Department of Energy (DOE) asked its fusion advisers to put together a team to analyze the current design. Interest in their work was heightened by recent advances in modeling that have raised questions about the efficacy of the ITER design (*Science*, 6 December, p. 1600).

As recently as 1995, program officials gave themselves a 2-in-3 chance of reaching ignition, a sustained burn, without injecting power from the outside. With an outside kick of about 100 megawatts, they said, the odds of reaching ignition rose to 99.5%.

The new report, by a team that included about 50 scientists and engineers not directly associated with the program, lengthens those odds. Although it concludes that there are no insurmountable obstacles to building and operating the machine, it paints a sobering picture of the difficult technical issues in its path. The problems range from removing tritium from waste water to the design of thermal blankets necessary to counter intense radiation. Long-pulse ignition "cannot be assured," it says, "but [it] remains a reasonable possibility." In the meantime, it states, important physics on plasma confinement could be accomplished even without ignition. And future upgrades could lead eventually to a self-sustaining burn.

How these findings play in the political realm may be critical in determining whether the project's next phase moves from paper to plasma. While other international partners have conducted reviews of the design, none was as comprehensive as the DOE study, and none has raised such detailed questions about the ability of ITER to reach ignition. "They boosted expectations before they had a design," complains one fusion researcher about the earlier, rosier predictions.

Reviewing a draft of the report last week before sending it on to DOE, members of the Fusion Energy Sciences Advisory Committee (FESAC) complained that it did not go far enough in diminishing those expectations. Several members argued that the document played down a series of problems outlined in the three detailed subpanel studies. "I do not believe there is adequate emphasis on the substantial uncertainties in the design," said Ira Bernstein, a Yale University physicist. "There seems to be too much positive spin," added Earl Marmar of the Massachusetts Institute of Technology's plasma-fusion center. Those arguments led FESAC to modify the report to convey a less optimistic tone.

The new language accurately reflects the steep road ITER must travel to achieve ignition, says DOE fusion chief Anne Davies. "The fusion community probably should have been more careful in its promises," she says about earlier pronouncements. And close scrutiny of those promises is far from over. The National Research Council, at DOE's request, is preparing a report on ITER's overall value to the United States that is due 1 December. In the meantime, ITER supporters are hoping that diminished expectations won't translate into diminished political support.

–Andrew Lawler