Innovations

Eek, a XenoMouse

Abgenix, Inc.

Chemistry & Biology 2000, **7**:R185–R186

1074-5521/00/$ – see front matter
PII: S1074-5521(00)00008-9

We cannot rebuild him. We do not have the technology.

Lee Majors will be long dead by the time we have a real six million dollar man, but the five and a half billion dollar mouse is already with us. It belongs to Abgenix, Inc. of Fremont, Calif. At a cost of at least $50 million dollars, the validation of the XenoMouse idea "was a pretty expensive experiment," says Raju Kucherlapati of Albert Einstein College of Medicine in New York.

But the payoff has been enormous. With Abgenix just passing its fourth birthday, and all its technology still tied in some way to the XenoMouse, Abgenix now commands a valuation of almost US$5.5 billion. All this for an idea that was hatched in a company called Cell Genesys, Inc. (Foster City, Calif.) that is itself valued just below a measly US$1 billion. Not a bad jump in value for a mouse that makes antibodies.

An idea is born

In a 1985 *Nature* paper Kucherlapati showed that mammalian genes could be modified by gene targeting. (This was extended to embryonic stem (ES) cells in 1987 by Mario Capecchi of the University of Utah.) "We began to think about how this technology could be commercialized," says Kucherlapati. "That led to the establishment of Cell Genesys."

The job of refining the three ideas that Cell Genesys would focus on (one being XenoMouse) fell to a group of scientists and two venture capitalists from the Mayfield Fund. Grant Heidrich, still at Mayfield, and Mark Levin, now CEO of Millennium Pharmaceuticals, Inc. (Cambridge, Mass.) "thought antibodies had great therapeutic opportunities and there weren't good ways to produce them," says Kucherlapati. "The stimulus was really from a business/financial point of view."

The scientific idea was to replace a mouse's immunoglobulin genes with human immunoglobulin genes. The mouse would still see human proteins as foreign, and could therefore produce antibodies against human disease targets. But those antibodies would be human, and would be recognized as self by humans. Unlike the first generations of mouse-derived monoclonal antibodies, these antibodies would not be rejected by the patient. Antibody half-lives would soar, allergic reactions would be avoided, and the tarnished promise of monoclonal antibodies finally realized.

Say hello to the (almost) six billion dollar mouse.

In 1991 Cell Genesys formed a limited partnership with JT America Inc., the American division of Japan Tobacco, Inc., to pursue the XenoMouse idea. JT put up ~$20 million to get the research going. "In retrospect that was a small investment," says Kucherlapati. But it was certainly not an investment with a guarantee of success. "Ideas are a dime a dozen," says Kucherlapati, "but you have to be able to show that they work." At Cell Genesys that task fell to Aya Jakobovits, who Kucherlapati describes as "a fantastic scientist — a real go-getter."

Making the mouse

Initially the researchers planned a wholesale replacement of human for mouse immunoglobulin regions. "Then we recognized that would be a huge task," says Kucherlapati. The compromise solution was to delete all six tandem J, or joining, regions from the single gene for the heavy chain immunoglobulins, and to delete a constant region from the major light chain gene. The apparatus that recombines different segments of DNA to create a final, expressed immunoglobulin gene cannot skip over any one class of segments, so mice with deleted J regions failed to produce either immunoglobulins or mature B cells.

The next task was to insert the human immunoglobulin genes. Easy enough, except that the DNA segments encoding the light and heavy chains weigh in at around 1.5 Mb each. Jakobovits' solution was to fuse yeast spheroplasts, carrying huge chunks of human immunoglobulin DNA on yeast artificial chromosomes (YACs), to mouse ES cells. Random integration of yeast genomic DNA did not appear to perturb mouse development, and integration of the YAC DNA led to mice that expressed human antibodies. After all that hypothesizing and money, here, says Kucherlapati, was "the real moment of triumph."

The finished product

The final XenoMouse was created after recombining, in yeast, four YACs to form a 1020-kb heavy chain YAC, and three YACs to form an 800-kb light chain YAC. Once the DNA was integrated, mouse enzymes carried out normal recombination and affinity maturation to produce functional antibodies. Each mouse is outfitted with a single IgG heavy chain constant region, so antibodies from some mice simply block an interaction, whereas those from other mice recruit immune effectors that may help kill a target cell.

While the XenoMouse was being created, other companies had been busy coming up with their own solutions. The simplest was to take an existing mouse antibody and replace large chunks with the corresponding human segments, while leaving the variable regions intact to preserve binding specificity. This procedure has led to commercial products, but it

takes time and can result in a loss of specific binding affinity.

The second alternative is phage display, in which peptides expressed on phage are panned for binding of antigen. Vast numbers of phage can be screened, but binding affinities in this procedure do not generally reach the levels seen in antigen–antibody interactions. Further loss of binding affinity is a great risk when transferring the peptide sequence to an antibody framework. Thus, phage display is suited more to finding low affinity reagents that can be used to test expression patterns or the effects of binding a certain protein.

Delivering the goods

The beauty of the antibody concept is the direct translation from target to clinical candidate. ''The mouse does all the work of making the molecule so you have many fewer people involved in the process,'' says Abgenix chief financial officer Kurt Leutzinger. Then, he says, the incredible specificity of the antibody means that ''we only have to show that the one thing [the antibody] binds to is safe enough to bind to. That really cuts down the time it takes to get into the first human trial.''

Seeing that process in action has made Leutzinger optimistic about the future. ''With a reasonable amount of work we think we can get to a steady state of two or three IND [investigational new drug] filings per year without becoming a huge company,'' he says. That stream of clinical candidates shouldn't overwhelm the company, says Leutzinger, because ''we operate [only] from immunization to phase II trials. With that focus we can handle a lot more products.''

The company has targets in phase I and II trials, although some of these targets are also being pursued by other companies. Recent deals with genomics companies are an attempt to remedy this situation by picking up some proprietary targets for in-house development. Meanwhile, Abgenix is generating income by licensing its technology to 20 collaborators who are working on more than 30 antigens.

Antibodies as a quick fix

Antibodies are good at targeting accessible molecules, such as soluble immune regulators and their receptors on circulating cells. But antibodies are also expensive drugs that need to be injected. According to Geoff Davis, the chief scientific officer at Abgenix, ''some of our big pharma partners are using antibodies as a quick entrée into the market, to corner market share. Certainly you will see some antibodies replaced by small molecules.'' But to Nils Lonberg, the scientific director at GenPharm International, Inc. of San Jose, Calif. (now a division of Medarex, Inc. of Princeton, New Jersey), ''a lot of that is wishful thinking.'' Whereas small molecules typically jam enzyme active sites, antibodies are more often used to interfere with protein–protein interactions. ''A lot of these antibodies,'' says Lonberg, ''will be around for a long time — a lot longer than many organic chemists expect them to be.'' Leutzinger agrees. ''We think that once antibodies are established in a market it will be hard to dislodge them with small molecules,'' he says, ''because the toxicity profile of small molecules is so much worse.''

Business ballet

The two things that make Abgenix stand out are a simple founding technology and an uncanny ability to extricate itself from unwanted contractual situations. The company's first and ongoing business achievement is the separation from its parent, Cell Genesys. The divorce began in 1996 when Abgenix was spun out. Cell Genesys now owns just 12% of Abgenix's stock after selling some holdings and dilution by further fund-raising. But, says Davis, ''they have over $200 million in the bank because of the last financing, and they still have a stake in Abgenix. At this point I think everyone is happy.''

Abgenix was originally spun out because its research did not fit with the new gene-therapy focus of Cell Genesys. ''I doubt that the technology would have blossomed under one roof with non-complementary technologies,'' says Davis. A similar rationale drove the separation from JT, which in December 1999 relinquished its 50% interest in XenoMouse intellectual property in return for what now seems a meager sum of $47 million. ''It was a fantastic set of events for Abgenix,'' says Kucherlapati. ''That is the genius of [CEO] Scott Greer and [chief business officer] Ray Withy — how they were able to navigate through those waters.''

The third challenge came from Lonberg and Robert Kay of GenPharm. They had independently conceived of and created their own version of the XenoMouse. Their injected plasmid constructs encoded fewer immunoglobulin variable regions than the Abgenix YACs, leading Davis to claim that the Abgenix technology is ''superior.'' But Lonberg claims that ''the quality of the antibodies does not seem to be dependent on the size of the DNA that [goes] into the mice,'' and notes that GenPharm now has mice with entire chromosome fragments.

Although Abgenix initiated litigation against GenPharm, the two sides soon reached an agreement allowing both to operate. Abgenix had to pay up, but once again got off cheaply. Lonberg, for one, says he ''didn't want to have a career in litigation.''

So now that Abgenix is free from constraints and rolling in money, how does it feel for the man who started it all? Not wanting to crow too loudly, Kucherlapati goes for understatement. ''I think,'' he says, ''we are happy.''

William A. Wells
1095 Market Street #516, San Francisco, CA 94103-1628, USA; wells@biotext.com