CLONING

Big business is high on the Honolulu method

Russ Hoyle

When the news broke in late July that Ryuzo Yanagimachi and Teruhiko Wakayama at the University of Hawaii (Honolulu) had successfully cloned 50 mice from adult cells, it was evident to many that cloning is here to stay. Coming only 17 months after the historic cloning of Dolly the lamb in Scotland, the Honolulu mice clones represented, among other things, a clarion call for watchful commercial interests to spring into action. Crowed Laith Reynolds, the commercial director of a new biotechnology spin-off called ProBio America Inc. (Honolulu), "This is the dawn of a new age in the scientific world."

Reynolds certainly had reason to hope so. ProBio, a U.S. subsidiary of Australia-based ForBio Limited (Brisbane, Queensland), was at the time busily putting the final touches on an agreement with the University of Hawaii's Office of Technology Transfer and Economic Development Office to provide Yanagimachi's research lab with $1 million to advance animal cloning and freeze-dried sperm technology (*Nature Biotechnology* 16:639–641, 1998). In exchange, ProBio gained access to international licensing rights for future pharmaceutical or biomedical products developed by the University of Hawaii researchers.

The ProBio deal will give Yanagimachi and the university as much as 50% of net proceeds for 20 years, including up to 8% of net sales, 25% of licensing revenue and payouts for milestones such as use of their technology to clone large commercially useful animals, from pigs and horses to cattle. The company's primary interest lies in developing animal clones for human cell and tissue therapy, including animal-to-human transplants.

The consensus among biomedical researchers is that the Honolulu mouse-cloning method is a significant step toward the successful cloning of larger mammals (see "Cloning experiment improvements," p. 809). The technique, developed by Wakayama, involves injecting the nucleii of adult cumulus cells into eggs from which genetic information had been removed. After some six hours—enough time for the egg to reprogram the cumulus cell DNA—the researchers chemically stimulated egg division. The Honolulu method reportedly allows researchers more precise control over the cloning results, though they have no idea precisely how the process of genetic reprogramming takes place.

By contrast, Wilmut's technique with Dolly, essentially fusing cells and mixing their contents, was comparatively haphazard. The Honolulu researchers reportedly grew as many as 17 fully developed mice from 800 cloned embryos, a 2.1 percent success rate-compared to one success in 223 tries for Dolly, or a rate of less than .5%. To paraphrase one skeptical scientific critic of recent cloning experiments, that still may be closer to "an anecdote" than "a result."

But it was enough to turn on the flow of venture capital. ProBio, which had been working with Yanagimachi's lab on freeze-dried sperm, immediately announced a licensing deal with PPL Therapeutics Plc (London), set up by the Roslin Institute in Edinburgh to commercialize cloning technology. PPL is interested in using the Honolulu method to clone pigs and use their organs for human transplants.

The deal was apparently a first step in ProBio's strategic plan to establish a worldwide consortium of resources to link research and development, commercialization and eventually the marketing of pharmaceutical, therapeutic and environmental uses of new animal reproductive technologies. ForBio Ltd, the Australian parent company and majority shareholder in ProBio, announced last month that it would reduce its holdings in the new company to 25% to encourage new investment capital. The move, said ForBio Chairman Neil Summerton, will allow ForBio to continue to focus solely on "the genetic improvement and cloning of high-value plantation crops such as trees, palms and coffee."

Indeed, if the corporate and academic ties ForBio has established in the field of innovative plant cloning technologies are any indication, ProBio's grand vision could provide a virtual roadmap to the commercial future of transgenic agricultural and therapeutic biotechnology. ForBio has pioneered the consortium concept by forging joint ventures and subsidiaries around the world to deploy its technologies.

ForBio currently holds the international licensing rights to DuPont's DNA marker technology RAPD, which allows scientists to select specific genes that enable them to construct new tissues with desireable traits. It is building a state-of-art robotic production facility in partnership with Monsanto in Indonesia to mass produce genetically "elite" hardwoods such as teak and acacia. In the U.S. it has teamed with Integrated Coffee Technology Inc. (Deleware, MD), an agbiotechnology company involved in the development and marketing of zero-caffeine coffee and coffee beans that ripen uniformly.

ForBio's academic associates include the forest biotechnology consortium at North Carolina State University (Raleigh, NC), the Salk Institute for Biological Studies (San Diego, CA), and the Forest Research Institute of Malaysia.

ForBio's aggressive international consortium strategy has reportedly placed it in the forefront of emerging large-scale commercial tree cloning industry. There is every reason to believe that ProBio executives—who presumably have access to ForBio's burgeoning network of technical and financial resources-are thinking along the same lines for the commercialization of animal cloning. ProBio's Reynolds is bullish on the Honolulu method. "There's an infinite number of uses for clones," he said.

Such a robust strategic vision, however—even for a technology that no one believes will begin to reach fruition for at least another decade—is virtually certain to be caught up in daunting ethical, political and regulatory controversies. For starters, there are serious scientific obstacles remain to be overcome. Besides the inevitable religious and ethical protests, the future of cloning pigs, for example, is clouded by genetically conveyed porcine endogenous retroviruses that may create serious health risks for transplant patients.

Researchers do not know whether or under what circumstances such viruses might prove harmful to humans. Unfortunately such scientific uncertainty in the past has proven a tremendous political target for opponents of biotechnology. Though cloning animal tissue might result in useful products such as human blood-clotting agents, growth hormones and treatments for diseases from cancer to cystic fibrosis, the perception of significant possible health risks could easily create a backlash against traditional public acceptance of genetically engineered therapeutic drugs.

Perhaps the most important consequence of last month's University of Hawaii mouse cloning should be some serious new thinking on the part of key federal agencies about the prospects of creating an effective regulatory system to provide standards for companies like ProBio as they set about developing potentially powerful new cloning technologies. ///