The rocky road to success

Tackling the legal and ethical minefield associated with human embryonic stem-cell research is not for the faint-hearted. **Erika Check** meets one man who is relishing the challenge.

Kevin Eggan has always been a climber. He grew up in the flat cornfields of Normal, Illinois, but every summer his father would take him mountaineering among the tall peaks of the Cascade Range in the Pacific Northwest. "Summer was nirvana in the mountains," Eggan says. "In the winter I would go back to school in Illinois, and I would just wait for the next summer to come along so I could go climbing again."

Eggan is now assistant professor of molecular and cellular biology at Harvard University. His passion for climbing may explain some of his success as a scientist, which his colleagues say is marked by two things: enthusiasm and a dogged determination to tackle the toughest problems in his field.

Eggan's next project could be his most challenging yet. This autumn he hopes to use cloning techniques on human cells to study conditions such as diabetes and Parkinson's disease — work that isn't being done at any other US university. But even as he prepares to begin these experiments, opponents are striving to ban them — and they are using some of Eggan's own findings to support their case.

Scaling the heights: Kevin Eggan's work and hobbies are characterized by enthusiasm and determination.

Bespoke cells

Working with developmental biologist Doug Melton at the Harvard Stem Cell Institute, Eggan wants to generate embryonic stem cells that match individual patients. To do this he will use a technique called somatic cell nuclear transfer — more commonly referred to as cloning.

Eggan will take a sample of skin cells from a patient, and will extract the nuclei from individual cells. Each nucleus will be transferred into a human egg stripped of its own genetic material. In theory, the egg will then divide and develop into an embryo containing only the patient's DNA. And in the process, the egg will reprogramme the nucleus back to its earliest state, which means that cells from the embryo should have the potential to generate all of the tissues in the human body.

Each of these embryonic stem cells will carry the distinctive genetic quirks of the patient who donated the skin cells. By studying these stem cells, Eggan hopes to understand why the donor patients became ill, and what might be done to cure them.

Eggan's introduction to this technique came seven years ago, when he joined Rudolf Jaenisch's lab as a graduate student at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. Jaenisch was starting up a mouse cloning project to study the genetic changes that make it possible for adult cells to be reprogrammed.

Eggan attacked this cloning project with zeal. "I thought it was the most exciting and coolest thing that I had ever seen," he says. But grim reality soon set in. Eggan shut himself in the mouse warehouse every day, seven days a week, for about a year. But he kept failing. He could make embryos, but they simply refused to develop any further than a single cell.

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What saved Eggan was his persistence — and his love of video games. He began to approach cloning the same way he had dealt with the classic arcade game *Super Mario Bros.* — by refusing to be beaten by a tricky stage or enemy. "There are people who really relish getting past that challenge, and they replay the game over and over and over and over again until they figure out exactly how to do it. That's the kind of person you need to be to succeed at nuclear transplantation," Eggan says. "And fortunately, that appealed to me." His determination eventually paid off and enabled Jaenisch's lab to publish a series of key papers

on cloning and its effects on cloned animals[1–3].

Melton, who was using human embryos left over from *in vitro* fertilization treatment to study disease, heard about Eggan's persistence from Jaenisch. He and Eggan met up and hit it off. "Kevin has this attitude that science can be fun," Melton says. "And he doesn't hesitate to do an experiment because it's too hard." The pair decided to start a project that would use cloning to produce new human embryonic stem-cell lines. The lines would be tailored to individual patients with diabetes and disorders of the brain and nervous system.

Private function

In 2002, the pair began the difficult task of securing funding and ethical approval for their project. Two separate measures bar the project from receiving funding from the US government. One, the Dickey Amendment, is passed by Congress every year and prevents scientists from using taxpayers' money to create or destroy human embryos for research, such as cloning. The second measure is a four-year-old executive order passed by President George W. Bush. It bans federal support for work on embryonic stem-cell lines created since 9 August 2001.

Melton is funded by the private Howard Hughes Medical Institute in Chevy Chase, Maryland, and last year, Harvard created the Harvard Stem Cell Institute, which will use money from other private donors to fund stem-cell research. With the money in the bank, Eggan and Melton are ready to begin their project. They are just waiting for a final approval from a Harvard ethics review board, which they hope to get this autumn.

In the three years it has taken to lay the groundwork for the cloning experiments, Eggan has tackled another challenge facing the stem-cell field: the shortage of human eggs. But in doing so he may have unwittingly played into the hands of those who want to ban work on human embryonic cells.

Cloning to produce stem cells requires human eggs. But few women want to endure the uncomfortable cycle of hormones and surgery that accompanies egg donation. In June, Eggan told a scientific meeting that he had developed a technique that may eventually solve this problem[4]. Eggan has created cells with properties similar to embryonic stem cells by fusing embryonic stem cells from existing lines together with skin cells. The embryonic stem cells seem to reprogramme the skin-cell nuclei just as eggs do.

Eggan calls his creations 'hybrids' — genetic remixes that act a lot like embryonic stem cells, but don't actually come from embryos. The paper describing the work appeared last month[5] — just as the US Senate was gearing up to debate embryonic stem-cell research. And so, perhaps inevitably, Eggan's findings have taken on a life of their own.

In May, the House of Representatives passed a measure to overturn the Bush restrictions on stem-cell research funding. The House bill would allow funding for research on stem-cell lines derived from embryos left over from *in vitro* fertilization procedures. The Senate is now considering passing that same bill — perhaps as early as this month.

R. HELLMISS-PERALTA/HARVARD UNIV.

"No one expected the social and political maelstrom over cloning to crescendo to this point. But as I've been around since the beginning, I've been able to cope with the gradual incline." — Kevin Eggan

The third way

But opponents of the work have seized on studies such as Eggan's as a possible third way out of the debate. They say that instead of overturning the Bush ban, the Senate should simply fund research that aims to make new stem-cell lines without creating embryos.

On 12 July, Leon Kass, a conservative bioethicist and chairman of the President's Council on Bioethics, lauded Eggan's work in the *Washington Post* on the morning of a crucial Senate hearing on stem cells. "Every public-spirited American should be encouraged by these findings. We should be hopeful that a technological solution to our moral dilemma might soon be found," he wrote. The publication of Eggan's paper only added fuel to the fire. On 23 August, the same newspaper quoted Senator Tom Coburn (Republican, Oklahoma), a physician who has led the opposition to embryonic stem-cell research: "All this is confirmation we will see breakthroughs without compromising ethical standards," he said. "We're not going to have to go that way if we can just be patient and fund the basic science."

Eggan says that these debates are misleading, because his work does not create substitutes for stem cells derived from embryos. The hybrids still contain two nuclei: one from a skin cell and one from an embryonic stem cell. So they have an abnormally high amount of DNA, and Eggan needs to work out how to remove the embryonic stem cell's DNA. Eggan adds that he has only just begun working with the hybrids, so it is not clear what they will or won't be able to do. "It's frustrating," Eggan says, "because they're implying that our work is a solution, which it is not yet. These are ideas in their most nascent stages."

However the hybrid research develops, Eggan will continue with his planned cloning experiments using private funds. But the political debates over stem-cell research could still threaten this work. Some in the Senate are pushing for legal bans on any kind of cloning, which would outlaw Eggan's experiments. These laws seem unlikely to pass at the moment, but their supporters raise the issue year after year.

All the controversy could make a young biologist wary. After all, it's difficult enough to get a scientific career off the ground, even without the threat that the government might ban your research. But Eggan is used to the controversy; he began graduate school in 1998, the year after scientists in Scotland announced the birth of Dolly the sheep, the first cloned mammal. "No one really expected the social and political maelstrom over stem cells and cloning to crescendo to this point," says Eggan. "But as I've been around since the beginning of all of this, I've been able to cope with the gradual incline."

No stranger to inclines of any kind, Eggan still finds time to indulge his passion for climbing. Last November, he celebrated his father's 70th birthday by joining him on a little hike — a 6,000-metre jaunt up Mount Kilimanjaro. ■

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