

# Geron gets green light for human trial of ES cell-derived product

After an eight-month delay, on 23 January, the US Food and Drug Administration (FDA) approved the first human trials of embryonic stem (hES) cells, a surprise decision that came on the eve of President Barack Obama's expected policy change concerning hES cell research.

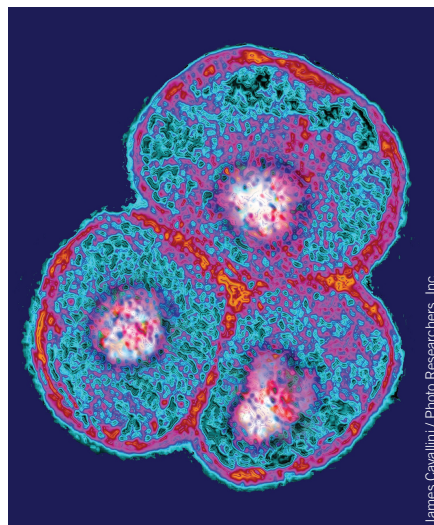
This summer, Geron Corporation of Menlo Park, California, will begin treating ten patients who have suffered a complete thoracic-level spinal cord injury in a phase 1 multicenter trial. The pioneering therapy is Geron's 'GRNOPC1 product', which contains hES cell-derived oligodendrocyte progenitor cells that have demonstrated remyelinating and nerve growth-stimulating properties.

For a company that held its ground during the Bush administration's assault on hES cell research, the FDA's clearance is part triumph, part vindication for sticking with the Sisyphean task of preparing a gargantuan 22,000-plus page Investigational New Drug (IND) application for their product. "There was plenty of crying going on here when we received notification that the FDA had cleared our IND," says Thomas Okarma, Geron's president and CEO.

Although they may not have shed tears of joy, many players in the budding regenerative medicine sector sounded a note of relief, and even optimism. "I've been talking to my colleagues in this field, and the overall feeling is that this is an important milestone because it means that FDA will approve clinical trials using human embryonic stem cells, and that, in fact, there is [regulatory] support for developing therapies based on embryonic stem cells," says Michael West, CEO of BioTime and Embryome Sciences, both in Emeryville, California, who cofounded Geron in 1990.

Other CEOs of stem cell firms are also upbeat: "Clearly, this opens the door not only for Geron, but other companies that develop strong IND packages for stem cell-based therapeutics. And given the compelling evidence that there's a reasonable chance for clinical success, this is a very positive development for the regenerative medicine field," says Richard Garr, president and CEO of Rockville, Maryland-based Neuralstem, which in December filed an IND to use human neural stem cells for treating amyotrophic lateral sclerosis. On the same day, StemCells, Inc. received approval to begin clinical trials of a purified human neural stem cell to treat Pelizaeus-Merzbacher disease—a fatal brain disorder that affects children.

But West, who spurred Geron's support for the research of human stem cell pioneers James



Embryonic stem cells. Companies are rapidly gearing up to follow in Geron's footsteps, as the firm receives the first approval to carry out embryonic stem cell work in humans.

Thomson and John Gearhart before leaving the company in 1998 and then ran Worcester, Massachusetts-based stem cell company Advanced Cell Technology (ACT) until 2007, says there's also a sense of unease with Geron's planned trial. "While we all want [the clinical trials] to work, there's a concern among many of us that some of these patients will develop ectopic growths, and that would be a disaster."

Ectopic growths, also known as teratomas, are encapsulated, usually benign tumors that may grow from residual hES cells. They can occur naturally, but the fear, based on some animal studies, is that some proportion of the cells derived from hES cells injected into the body could stray from their intended developmental pathway. Last month, a group of Israeli researchers reported that a boy with ataxia telangiectasia who had received several fetal neural stem cell transplants developed teratomas in his brain and spinal cord four years after treatment (*PLoS Med.* 6, e1000029). "Concerns about tumorigenicity are bang on," says Melissa Carpenter, a San Diego-based independent consultant on stem cell therapeutics. "Yes, Geron and others have done extensive testing in rodents that show that teratomas don't form from their preparations, but a rat's lifespan is short. What we really don't know is how these cells will behave in a human that might live 10–50 years after receiving treatment."

Although acknowledging that teratoma formation might be a concern, Geron's Okarma

## IN brief

### Alnylam dealt blow

The European Patent Office (EPO) has revoked a patent covering RNA interference (RNAi) technology from Alnylam Pharmaceuticals. The '945 patent (EP 1214945), which belongs to the Kreutzer-Limmer patent family, protects the use of small interfering RNAs 15–49 nucleotides long. Alnylam's claim was disputed by London-based Silence Therapeutics, Abbott Park, Illinois-based Abbott and San Francisco-based Sirna, owned by Merck. The ruling—made in part because the patent was deemed too broad—is not final and will be appealed. "In an area like this, companies don't expect to get their patents through unobjected to," says patent lawyer Simon Cohen, of Taylor Wessing, a European law firm. "They start off with broad claims and they realize they have to narrow down their scope." Cambridge, Massachusetts-based Alnylam had another of its Kreutzer-Limmer patents revoked by the EPO last December. A spokesman for Silence Therapeutics says the whole Kreutzer-Limmer patent series may eventually fall, creating space for other companies who want to work with RNAi. This is "very much the start of litigation and opposition, rather than the last phase of it," Cohen stresses. In the US, Alnylam received recent FDA approval for phase 1 trials of an RNAi-based treatment for liver cancer.

Asher Mullard

### C-Path sets diagnostics standard

A newly launched diagnostics evaluation service for companies could help standardize tests and ease their transition to market. The United States Diagnostic Standards (USDS), a nonprofit organization set up by the Critical Path Institute (C-Path), will provide independent test evaluations, effectively functioning as a voluntary "Underwriters Labs" for diagnostics companies, says Jeffrey Cossman, chief scientific officer at C-Path, of Rockville, Maryland. Analytic evaluations performed by the new entity will take place at carefully selected neutral sites. Under USDS policy, the clinical samples (e.g., blood, tumor tissue) used as standards in the evaluation of diagnostic assays must be approved by an independent, outside panel of experts. In some instances, well-established clinical samples may serve as standards so that assays from different suppliers can be compared. Although the group has no regulatory authority, diagnostic test manufacturers can use evaluation results to support an application for FDA approval. Alternatively, as one of its many services, the USDS will certify a Laboratory Developed Test (LDT) and ensure its performance. As Cossman explains, "The information [USDS provides] would be useful for [insurance] payers, clinical pathology laboratories, providers, as well as for regulators such as FDA, [and] might help with reimbursement decisions, as well as approval or assurance that an LDT (not evaluated by FDA) performs as labeled."

Jim Roberts

## IN brief

## Vatican cheers GM

A closed door meeting to be held at the Vatican in Rome in May will see leading scientists gathering to discuss a campaign backing agricultural biotech. The study week has been organized by Ingo Potrykus, co-inventor of the fortified Golden Rice technology and president of the Golden Rice Humanitarian Board, on behalf of the Pontifical Academy of Sciences. The Vatican has long been concerned about food security, and advisors from the academy, which holds a membership roster of the most respected names in twentieth-century science, have recognized that plant biotech has the potential to benefit the poor. "I think we are heading in the right direction with this meeting and it will help to dispel some of the myths about GM crops," argues Peter Raven, director of the Missouri Botanical Garden in St. Louis and an academy member. Participants are expected to issue a definitive declaration and work on a roadmap for science-based regulations for genetically modified (GM) crops. "I would hope the moral high ground of the Vatican is relevant at least in Catholic countries," says Potrykus, whose Golden Rice project has been held up by political hurdles. It will be particularly interesting to see reactions in Italy, where a nine-year ban on open field trials recently ended. Some of the 'regions', into which Italy is subdivided, "still jeopardize field studies by failing to identify [planting] locations," says Piero Morandini of the University of Milan.

*Anna Meldolesi*

## China overhauls patent law

China's top legislature has amended its patent laws in a bid to support domestic innovation and entice foreign biopharma companies to do business in the country. The revised law, passed late last year by the Standing Committee of the National People's Congress, will take effect on 1 October. The intent is to raise the novelty benchmark by requiring that a patent application must be new worldwide. In the past, patents could be granted as long as the technology was novel in China. The revised law will allow inventors to apply for patents in other countries before obtaining them domestically. They must, however, first get an approval from China's patent administration department, which will determine whether the invention should be made a 'national secret'. The development is welcomed by the international patent community, says Michael Vella, head of the Shanghai-based China Intellectual Property Practice. "It is a signal that China's patent law is increasingly brought into line with international standards." The revised law should encourage foreign companies to do business with China, says Vella, by increasing patent enforcement. The new law also allows the granting of a compulsory license in cases of national emergency, and includes a provision requesting that patent applicants disclose the source of materials to affirm that they are lawfully obtained. "China will be the first major economic power that requires this," says Vella.

*Jane Qiu*

says those worries are misplaced because of the extensive purification steps that the company takes to produce hES cell-derived oligodendrocyte progenitor cells. "These aren't totally undifferentiated cells, but rather, they are 90% of the way to being a glial cell. Getting the cells to that state is a critical part of the manufacturing process, and it's integral to every product we're developing."

The bigger worry is that any safety issues that arise during Geron's clinical trial could have a devastating impact on the ability of stem cell companies as a group to raise funds. "We do worry about the potential negative impact a safety signal could have in this trial on the investment community, particularly among those investors that don't have a lot of history in the regenerative medicine space," says Joseph Pantginis, senior vice president at Merriman Curhan Ford in San Francisco. "Safety is obviously an issue, but having said that, you just have to look at the 22,000-page IND to see that the company went out of its way to address the potential for adverse events." And on a lighter note, Neuralstem's Garr adds, "The venture capital community hasn't been in this space for years, so I don't worry about scaring anyone off should Geron's trial run into trouble, which I actually don't expect."

Safety concerns aside—and the verdict will be out until phase 1 trials are complete in late 2010 or early 2011—researchers and investors alike worry that Geron's hES cell-derived oligodendrocyte progenitor cells simply won't work. "It's hard to think of an indication more difficult to treat than severe spinal cord injury in a human," says Aileen Anderson of the University of California, Irvine, who has had some success in using stem cells to treat spinal cord injury in rats. One issue is that the rodent spinal cord and primate spinal cord differ markedly both functionally and physiologically, "so extrapolating from rats to humans is not straightforward," she explains.

Of particular concern, says Arnold Kriegstein of the University of California, San Diego, is the fact that patients can experience some improvement in function without treatment, and so unless the positive effects of stem cell treatment are marked, phase 1 results could prove equivocal. "There's a real problem for Geron in that there is no way to track the fate of these cells once they are injected into the patient," he explains, "so in the absence of a big clinical response, which I'm not expecting, we may not get an answer as to whether this approach works or not."

Then there is the matter of perception and hype. On the day Geron announced the trial, the company's phone system crashed under the influx of calls from patients wanting to take part in the clinical trials. "This is a landmark study, potentially game changing, but expectations need to be realistic," says Pantginis. "We can't expect people to get up and walk following this therapy. Even the most optimistic of us don't expect that to happen." Indeed, experts such as Kriegstein, Carpenter and Anderson all agree that an improvement in lower body sensation or bladder control would represent huge benefits to patients.

In the meantime, Geron and others, including Neuralstem, BioTime, ACT and Stem Cells in Palo Alto, California, are pushing ahead with other stem cell-derived products, and Carpenter, for one, believes that everyone in the field owes Geron a debt of gratitude. "Geron has had such a difficult road," she says. "The company has been in the spotlight for years and it's been criticized up and down, but to its credit, it persevered, and as a result, everyone in the field is benefitting. And despite the safety concerns, the bottom line is that this trial is not premature. The safety of Geron's stem cell product has been tested as well as the current animal models allow. The next step is to take these stem cells into humans."

*Joe Alper Louisville, Colorado*

## SELECTED research collaborations

| Partner 1                    | Partner 2                                   | \$ (millions) |
|------------------------------|---|---------------|
| Micromet (Munich)            | Bayer Schering Pharma (Leverkusen, Germany) | 395           |
| Santaris (Horsholm, Denmark) | Wyeth (New York)                            | 100           |
| Arcadia (Davis, California)  | Advanta India (Bangalore)                   | *             |

\* Not disclosed.