NEWS

FDA to vet embryonic stem cells' safety

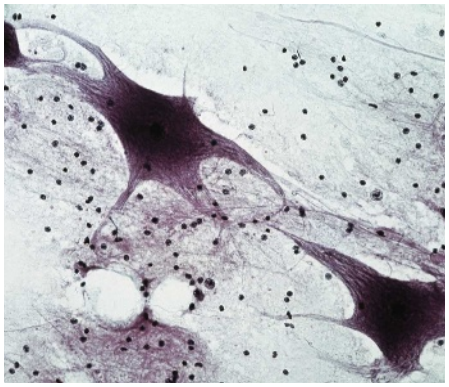
Investors, biotech companies and other stem-cell stakeholders are meeting in Gaithersburg, Maryland, this week for the US Food and Drug Administration's (FDA's) first public hearing on the safety of therapies that use human embryonic stem cells.

The meeting is "a big deal", says Michael Werner, former chief of policy at the Biotechnology Industry Organization in Washington DC. "It could provide clues about what the FDA is thinking in terms of product approvals."

Stem cells derived from human fetal and adult tissues are already being used in clinical trials. But researchers want to use embryonic stem (ES) cells because they show greater capacity to proliferate and differentiate into other cell types. Cells derived from human ES cells have shown dramatic results in treating animal models of disease, but they have not yet been tested in patients, and there are fears that they may carry health risks.

Geron, a biotech company based in Menlo Park, California, plans to start a trial in patients with acute spinal-cord injury this summer using oligodendroglial progenitor cells derived from ES cells. Two other California-based biotech companies, Novocell in San Diego and Advanced Cell Technology in Los Angeles, are also preparing to start human trials using ES-cell-derived products to treat (respectively) diabetes and visual impairment caused by macular degeneration.

The FDA seems to be most concerned about the cells' potential to cause tumours or to differentiate in dangerous ways, and whether the animal safety tests that have been carried out so far provide enough evidence to justify testing ES cells in people, according to FDA briefing documents seen by *Nature*. Another issue concerns how patients should be monitored for signs of problems. Members of the advisory committee have been asked not to speak to the press before the meeting.



M. KAGE/SPL

Geron plans to use human embryonic stem cells to treat patients with acute spinal-cord injury.

The FDA has been looking at these issues for a number of years, according to Michael West, head of BioTime, a biotech in Emeryville, California, and a former executive of Geron and Advanced Cell Technology. "The first time I met with them was in 2001 and they had given it a lot of thought back then," he says.

Human trials will not administer actual ES cells, but cells derived from them, and one of the biggest issues is how to assess the final cell product. One question is how many partially differentiated or undifferentiated cells, if any, are acceptable, and whether undesirable cells can be reliably detected. "You might have cells destined for the spinal cord mixed in with precursor cells destined to make a wisdom tooth," West says. "What happens when you put those cells into the spinal cord?" West says he's not against clinical trials, but he points out that the FDA has a very difficult balance to strike.

No decisions will be made at the meeting, but the process should eventually lead to guidelines from the FDA about required preclinical studies, trial design and patient follow-up, says Marie Csete, chief scientific officer at the California Institute for Regenerative Medicine (CIRM). This will be of great interest to investors, who hope to gain clues about the FDA's expectations. "The greater clarity the FDA can provide around those kinds of rules the easier it is for me to evaluate [ES cells] as an investment opportunity. Right now it isn't clear," says Gregory Bonfiglio of Proteus Ventures, which invests in regenerative medicine companies.

Csete describes the meeting as "a necessary first step" in bringing stem cells to the clinic within a well-regulated environment. CIRM, she says, will expect investigators it funds to implement scientific plans that lead to clinical trials, and she hopes this meeting will indicate what *in vitro* and animal work should be done. "We want to make sure that all the appropriate studies are considered that assure that human ES-cell-derived cell products are optimized for function and safety." ■

Monya Baker

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Advanced biofuels face an uncertain future

In trying to assure the market that there is a future for advanced biofuels, the US Congress may have gone too far. Its 2007 mandate for the production of such fuels, intended to convince technologists that a substantial market was guaranteed, may in fact be hampering the technology's development. The targets are so ambitious that many now expect them to be cut back, thus creating an uncertainty just like the one Congress intended to dispel.

Several companies are moving forward with demonstration plants — partially sponsored by the US Energy Department — to produce ethanol from cellulose in corn (maize) stover (the leaves and stalks), wood chips and other plant materials, rather than from the edible part of crops such as corn. But industrial-scale plants remain on the distant horizon, because the technique for efficiently making 'cellulosic ethanol' is still in its infancy. That has many wondering whether the investments are being made to meet the federal mandate, which ramps up to nearly 4 billion litres annually by 2013 and some 60 billion litres annually by 2022.

The biofuels community is watching the Environmental Protection Agency (EPA), which is developing regulations to certify that all of the biofuels in the programme reduce greenhouse-gas emissions by specific levels.

Add the continuing questions about actual production costs for a host of new technologies and long-term questions about the price of oil, and the result is a truck-load of uncertainty, says Wallace Tyner, agricultural economist at Purdue University in West Lafayette, Indiana. "What many people do in this situation is run," Tyner says. The repercussions could be huge if corn ethanol fails as a bridge to cellulosic ethanol. "If oil prices stay high, there's a real temptation to just keep growing corn rather than take the risk on cellulose."

Corn-ethanol production has skyrocketed in recent years, far exceeding the required production. Capacity is expected to hit nearly 40

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Chemical weapons agency shifts focus

Advances in science and changes in the pharmaceutical industry are producing new threats to the international Chemical Weapons Convention, experts warn.

Diplomats from the 183 countries that are signatories to the convention are meeting in The Hague, the Netherlands, on 7–18 April to review the 11-year-old convention, which is generally regarded as a success. To date, implementation of the convention has focused mainly on eliminating existing chemical weapons, although both the United States and Russia will probaby miss their 2012 deadline. The emphasis will soon switch to preventing future production.

One threat to the convention is the pharmaceutical industry, which is building more sophisticated facilities that could easily be converted to produce chemical weapons. And many of these facilities are in countries without established regulatory procedures, according to the Organisation for the Prohibition of Chemical Weapons, the watchdog that oversees implementation of the convention. Such sites should be monitored more closely, it says.

There are around 4,700 sites the organization calls other chemical production facilities (OCPFs) — which make everything from fertilizers to drugs — even though they do not produce chemicals on the convention's list of controlled agents. "Because of their characteristics and design, a good number of these facilities could quickly convert to the production of toxic chemicals if anyone so wishes. That makes them an object of particular interest," the organization's director-general, Ambassador Rogelio Pfirter, told *Nature*. Only around 10% of these sites have been inspected, and in some countries with large numbers of such facilities, just 1% have been inspected.

P. PSAILA/SPL

Special facillities have been set up to dispose of chemical weapons.

In a report released last week, the technical secretariat of the organization says that the agency "remains apprehensive about the present insufficient level of verification" of such facilities. Even though the number of inspections has increased, the effort "still does not provide a sufficient level of assurances for non-proliferation purposes", the report warns. The inspection effort has been hampered by the vast number of OCPFs and the fact that the organization generally relies on host countries to provide information on them, the report says. A new way of selecting sites for inspection is now being implemented, Pfirter says.

A number of countries attending the meeting are expected to agree that the agency should shift its focus from facilities making scheduled agents to OCPFs. However, developing nations such as China, which has a large number of OPCFs, may oppose such a move.

Other key concerns cited by the organization involve the "inexorable march of science and technology" including the growing interface between chemistry and biology and new technologies being developed. Microreactors, for instance, can produce more than 30 tonnes of potential chemical weapons agents a year, including phosgene gas, which was used in the First World War.

"This trend to a more versatile industry means that some of the underlying assumptions we had in the verification system developed in the 1980s may no longer apply," says Ralf Trapp, chemical disarmament consultant and former secretary of the organization's science advisory board.

"If someone were to open a chemical weapons programme today he or she would be looking at those developments, not only at traditional agents," Trapp says. ■

Daniel Cressey

billion litres annually this year and more than 51 billion litres annually in 2009, according to the Renewable Fuels Association, a trade body based in Washington DC. It comes at a time when corn ethanol is facing increased scrutiny. The mandate requires that corn ethanol reduces greenhouse-gas emissions to 20% below gasoline emission levels, but many researchers now believe that it will come up short. This is partly because the resulting higher commodity prices could drive agricultural expansion into wild lands around the globe.

Existing plants were 'grandfathered' in, meaning they won't have to meet the new environmental standards. Given that corn ethanol was capped at 57 billion litres in the mandate, this question affects 10% of the corn-ethanol market. But the entire mandate for cellulosic ethanol — which must reduce emissions to 60% below those of traditional fuels — rides on how the EPA calculates carbon emissions, including potentially indirect effects from land-use changes in the US and abroad. "All eyes are on the EPA to see how they resolve these questions," says biofuels expert Liz Marshall at the World Resources Institute in Washington DC.

"All eyes are on the Environmental Protection Agency at this point."

The industry must also address various infrastructure issues. Corn-ethanol production will soon reach what is known as the 'blending wall' by saturating the current market given the 10% cap on ethanol blends and the scarcity of stations selling an alternative fuel that is 85% ethanol.

David Berry, a principal with the venture-capital firm Flagship Ventures in Cambridge, Massachusetts, says that it will be "incredibly difficult" to meet the mandate for cellulosic fuels. It is likely to be refined and adjusted in the coming years, but this doesn't mean that it will go away entirely, so the technological front runners will be rewarded regardless. "Whether it turns out to be a US$15-billion-dollar market or an $80-billion-dollar market, those are still big numbers," Berry says. He believes that investors will make their move in the next couple of years after the results from various demonstration-scale projects come on line. "We have to figure out who the winners and losers are from a technical standpoint." ■

Jeff Tollefson