NEWS IN FOCUS

DANIEL ACKER/BLOOMBERG/GETTY

Monsanto could face a loss of revenue from its herbicide-resistant soya beans.

BIOTECHNOLOGY

Seed-patent case in Supreme Court

Loss of patent control could rekindle 'terminator' technology.

BY HEIDI LEDFORD

A technology called a 'terminator' was never going to curry much favour with the public. But even Monsanto, the agricultural biotechnology giant in St Louis, Missouri, was surprised by the furore that followed when it announced that it might acquire a method for engineering transgenic crops to produce sterile seed, which would force farmers to buy new seed for each planting. In 1999, Monsanto's chief executive pledged not to commercialize terminator seeds.

The concept, if not the technology, is now gaining traction again. This week, the US Supreme Court hears arguments that pit Monsanto against 75-year-old Indiana soybean farmer Vernon Hugh Bowman, who used the progeny of Monsanto seeds to sow his land for eight seasons. The company says that by not buying seeds for each generation, Bowman violated its patents. If Bowman wins — and observers say that is not out of the question — the decision could make it harder for biotech firms to enforce patents on engineered organisms, from seeds to microbes, prompting them to revisit terminator-like technology.

"If I were at Monsanto and I learned that patents are not available to protect my soybeans, I would think of some kind of technological fix," says Christopher Holman, an intellectual-property specialist at the University of Missouri-Kansas City School of Law. Indeed, some synthetic-biology companies, concerned about policing illegal, copycat proliferation of their technology, are already working on terminator-like safeguards.

Bowman was a regular customer for Monsanto's herbicide-resistant soya beans for his main crop, but bypassed the company by purchasing seed for a late-season crop from a grain elevator known to contain Monsanto's transgenic seed. In 2007, Monsanto sued him. As the case climbed through the court system, it grew from a simple contract violation to a challenge of the idea that companies can use patents to limit the offspring of naturally 'self-replicating' technologies. The lower courts sided with Monsanto, and many were surprised when the Supreme Court took up the appeal.

Even if the Supreme Court does not overturn the lower courts' rulings outright, biotechnology firms are bracing themselves for clarifications of patents on self-replicating inventions. Without that protection, companies say, they have little recourse to prevent someone from buying seed — or a cell culture or a transgenic animal — and using it to generate thousands more to sell again at a fraction of the original price. "Once you have sold the first seed, you are done," says Hans Sauer, deputy general counsel for intellectual property at the Biotechnology Industry Organization, a lobby group in Washington DC.

Early patents on 'gene-use restriction technologies' — later rebranded as 'terminator' technology by activists opposed to them — described a genetic modification that switched on production of a toxin that would kill off developing plant embryos. The result: a seed that could be harvested for food but would not produce offspring. The controversial proposal raised concerns that it would make farmers dependent on industry for their livelihood.

There are alternatives to making sterile seeds (see 'Terminator, the sequel'). One tactic would be to switch off the transgene of interest in seeds, so that they could grow into new plants but would not pass on the benefits of the engineered trait. Another approach is to place the transgene under the control of a switch that must be activated by a proprietary chemical. That would give companies control over the engineered trait by forcing buyers to return each year to purchase the chemical.

That is the strategy of Ginkgo BioWorks, ▶

a four-year-old synthetic-biology company in Boston, Massachusetts, that develops 'made-to-order microbes' to churn out marketable chemicals. Founder Jason Kelly says that the company plans to charge customers on the basis of how much they use the microbes. For accurate billing and theft protection, Gingko needs to control that use, so it is developing what Kelly calls a 'gene-guard' technology: a genetic tweak that makes production of the desired chemical dependent on a proprietary additive, supplied by Ginkgo, in its fermentation medium. The approach could even be used in nanotechnology, by making engineered nanobots that are dependent on a proprietary raw material.

In a strange twist of fate, terminator technology has begun to look more appealing to environmentalists. Organic farmers want ways to keep genetically engineered crops from contaminating their fields, and food-safety groups are concerned about contamination of food crops with products from a new generation of crops engineered to produce chemicals or pharmaceuticals. By ensuring that genetically modified plants survive for only one planting, "that technology would have alleviated a lot of environmental concerns", says Holman.

Approaches dependent on switching will take considerable research, however; companies reported technical challenges with the first generation of terminator techniques. Patents owned by Monsanto required the insertion of three different genes into the plant genome. Monsanto says it is currently not researching the techniques, and other companies are hoping that they will not have to. "Perhaps these technologies could provide new ways to protect investments," says Brett Lund, former head of intellectual property for the biofuels group of Syngenta, an agri-giant headquartered in Basel, Switzerland. "But the easiest and best way is through our patent system." ■

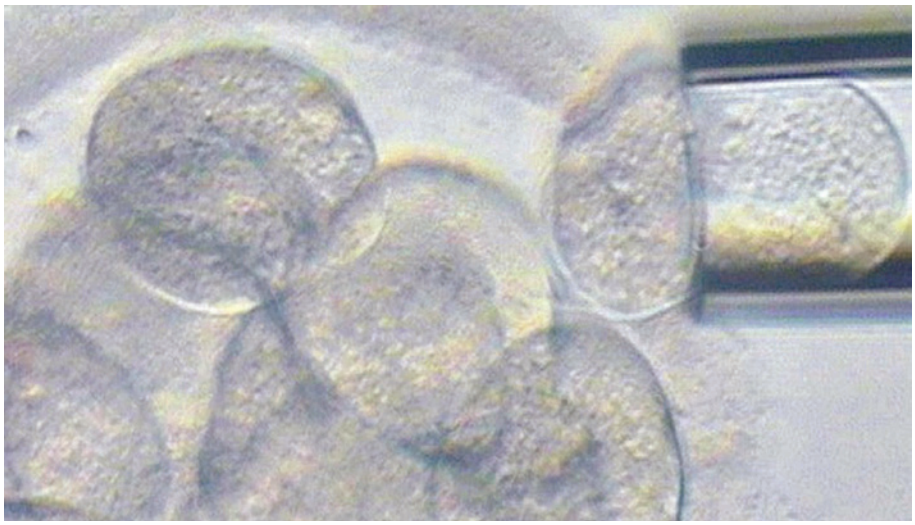
TERMINATOR, THE SEQUEL

As the US Supreme Court hears a controversial gene-patent case, biotechnology companies are once again considering ways to limit naturally self-replicating technologies.

SEEDS
'Terminator' technology produces sterile seeds.
Status: Politically toxic.

SYNTHETIC BIOLOGY
'Gene guard' needs proprietary supplement in growth medium.
Status: Under development.

NANOTECHNOLOGY
Requirement for proprietary supplement to 'grow'.
Status: Hypothetical.



TRACEY GRIFFITHS

Single-cell genomics is allowing fertility clinics to screen embryos for abnormalities more cheaply.

GENOMICS

Gene sequencing leaves the laboratory

Maturing technology speeds medical diagnoses.

BY ERIKA CHECK HAYDEN

The steep fall in the cost of sequencing a genome has, for the moment, slowed. Yet researchers attending this year's Advances in Genome Biology and Technology (AGBT) meeting in Marco Island, Florida, on 20–23 February are not complaining. At a cost as low as US$5,000–10,000 per human genome, sequencing has become cheap and reliable enough that researchers are not waiting for the next sequencing machine to perfect new applications in medicine.

Two recent beneficiaries: embryo screening after *in vitro* fertilization (IVF) and metagenomic medicine, which entails sequencing many different microbes en masse and then teasing out individual genomes to diagnose which ones are helping or harming human health. "The field is maturing," says geneticist Jay Shendure at the University of Washington in Seattle.

At last year's AGBT meeting, Oxford Nanopore, based in Oxford, UK, electrified researchers by unveiling details of a machine that could sequence DNA at unprecedentedly low cost and high speed — but that machine has not yet arrived on the market. This year, no splashy new technologies are expected. Instead, the HiSeq machine, made by Illumina, based in San Diego, California, has tightened its grip on the top end of the market (see 'Reasonably priced genomes'). Borrowing a metaphor from computer-circuit development, quantitative biologist Michael Schatz at Cold Spring Harbor Laboratory in New York says that after many "tick" years of dramatic technological innovation, the field is now in a "tock" period as researchers fine-tune the technology and expand it into applications.

One application depends on single-cell genomics, a focus of this year's meeting. To sequence a genome from a single cell, the DNA has to be amplified, a process that can introduce errors into the sequence. But new amplification techniques now allow accurate sequences to be obtained from individual cells, including the precious cells extracted from human embryos.

At the meeting, Dagan Wells at the University of Oxford, will describe how the technique can be used to select which of the embryos created by IVF has the best chance of developing into a healthy baby. Fertility experts already screen embryos for genetic abnormalities by extracting a single cell from each eight-cell embryo and running a variety of tests to detect chromosomal abnormalities, but this can cost around a thousand dollars per IVF cycle.

Instead, Wells extracts DNA from the sampled cell, amplifies it and sequences a part of the genome using the Personal Genome Machine, a fast sequencer made by Ion Torrent in Guilford, Connecticut, a subsidiary