FDA makes drug data public

The US Food and Drug Administration (FDA) has launched a pilot program that will share information from several recent product approvals aimed at helping scientists, companies and the public understand how the agency arrives at its approval decisions. FDA Commissioner Scott Gottlieb announced the initiative at a forum on FDA transparency held January 16 at Johns Hopkins Bloomberg School of Public Health. The agency will make public selected clinical information related to up to nine recently approved drugs. The drug makers voluntarily signed up to the program and agreed to provide detailed summaries, or 'clinical study reports' (CSRs), containing methods and results of the clinical reports submitted to the FDA. The pilot program comes after calls in recent years for regulators to be more transparent through release of clinical data (*Nat. Biotechnol.* **32**, 528–535, 2014). "We expect that making a CSR publicly available after a drug's approval will provide stakeholders with more information on the clinical evidence supporting a drug application and more transparency into the FDA's decision-making process," Gottlieb said in a statement. In his January 16 speech to the forum, the commissioner also said the agency is looking to "release additional information from complete response letters (CRLs) related to clinical safety and efficacy that could have significant public health value." CRLs are sent by the agency to manufacturers informing them that their drug application is not yet ready for approval. At his April 2017 confirmation hearing, Gottlieb said that he was open to releasing partially redacted CRLs to enhance transparency. *Jordan Hindson*

"What is remarkable is we have not seen it before. We were surprised but shouldn't have been. If you push the dose of anything high enough, you are going to see toxicity." James Wilson, of the University of Pennsylvania, was commenting on the recent report of animal deaths in a preclinical test of a high-dose gene therapy being conducted by Solid Biosciences of Cambridge Massachusetts. (*MIT Technology Review*, 31 January, 2018)

"We'd been chasing these shiny baubles. We hadn't talked about what we'd licensed to others—to people who can do later-stage development." Jim Neal, Xoma's CEO, talks about investor enthusiasm for the company's shift from R&D-focused biotech to asset manager, the stock rose 745% (from $4.20 to $35.51) over 2017. (*San Francisco Business Times*, 25 January 2018)

"ABBV [AbbVie] up 8% today, largely by making huge sums off an old drug and getting taxed less for it. I like their late-stage pipeline, but I find this a bit ridiculous," tweeted John Carroll, 26 January 2018.

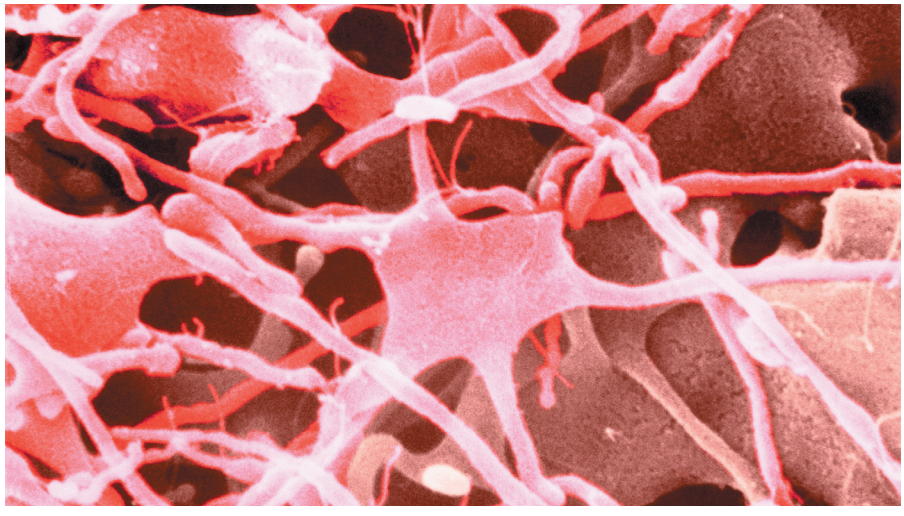
First off-the-shelf mesenchymal stem cell therapy nears European approval

Almost as soon as TiGenix gained the European regulator's recommendation for its allogeneic adipose-derived mesenchymal stem cell (MSC) therapy to treat complex perianal fistulas in Crohn's disease, its partner Takeda moved to strike a deal. On December 15 the European Medicines Agency (EMA) recommended approval of Leuven, Belgium–based TiGenix's treatment Alofisel (darvadstrocel; Cx601). A couple of weeks later, on January 5, the Osaka, Japan–based Takeda put on the table a €520 ($626)-million all-cash bid for the biotech. The other big winner is Melbourne, Australia–based Mesoblast, which used its strong patent position in mesenchymal stem cell therapy to strike an intellectual property (IP) licensing deal with TiGenix, under which it will obtain payments of up to €20 ($24) million plus single-digit-percentage royalties on all Alofisel sales.

If approved, Alofisel will be Europe's first allogeneic mesenchymal stem cell therapy, as well as the first product to gain approval in two decades for a condition that is notoriously difficult to treat. About 20% of Crohn's disease patients develop perianal fistulas, which are open channels that develop between the rectum or anal canal and the skin in the vicinity of the anus. They leak pus, stool and blood, and are very painful and debilitating. Complex fistulas—which account for over 70% of the total—involve two or more such openings and are even more difficult to treat than simple fistulas, which involve a single tract. Antibiotics, immunomodulators and tumor necrosis factor α (TNF-α) inhibitors are routinely used, but relapse rates are high, while long-term remission is rare (*Lancet* **388**, 1281–1290, 2016).

According to recently published Alofisel data from a 52-week pivotal trial in over 200 patients, 56% of those who received the locally administered cell therapy on top of standard-of-care treatment attained combined remission—defined as the closure of all treated external openings exuding material at baseline, and the absence of perianal abscesses as assessed by blindly administered MRI. Just 39% of those who received standard of care plus placebo attained similar remissions (*Gastroenterology* doi:10.1053/j.gastro.2017.12.020, 2017). The high placebo response "was not at all unexpected," says Steven Wexner, chairman of the department of colorectal surgery at the Cleveland Clinic Florida in Weston. All patients received standard of care and those in the control arm, moreover, may have benefitted from a preparatory procedure to clean out debris and other material from the open tracts, which was performed three weeks before treatment.

The study's biggest shortcoming was the high rate of dropout—about 35–40%—across the two treatment arms. Even so, Alofisel is almost as effective as certain surgical procedures, says Wexner, but without the risk of causing muscle damage that could result in anal incontinence. The most effective surgical approaches—there are about a dozen in all—can be the most problematic. "The



Don W. Fawcett/Science Source

Mesenchymal stem cells, a collection of cells with fibroblast-like features, are mostly isolated from umbilical blood, bone marrow or adipose tissue.

procedures that are least disruptive of muscle have the lowest rates of incontinence," says Wexner. Alofisel, which works through an incompletely understood immunomodulatory mechanism, is administered by injection to the tissue surrounding the fistula as a single dose of 120 million adipose-derived mesenchymal stem cells. In contrast, Remicade (infliximab), the only other therapy approved for treating fistulas in Crohn's, is administered systemically. It offers modest efficacy—it was approved on the basis of a 50% reduction in draining fistulas—but at the same time exposes patients to the risk of serious infection. "I think you'd be really hard pressed to justify giving an anti-TNF-α [antibody] solely if the problem was perianal fistula and a treatment as innocuous as this was available," says Wexner, who is surgical coordinator for the North American clinical sites participating in TiGenix's global phase 3 trial of Alofisel.

A US filing is still some way off. A positive read-out from the present global trial in 2020 would feed into a biologic license application in 2021. However, Alofisel may be able to seek conditional approval with the European data, under the US Food and Drug Administration's new regenerative medicine advanced therapy (RMAT) pathway. "That would allow us to submit in the first half of 2019," says Claudia Jiménez, senior director of investor relations and corporate communications at TiGenix.

Alofisel's imminent approval in Europe represents the second time TiGenix has made history in its home region. In October 2009, it became the first company to secure approval for an autologous cell therapy under EMA's advanced therapy medicinal product pathway, with the cartilage repair therapy ChondroCelect. That achievement proved to be a false dawn, however, as the product was a commercial failure because it struggled to obtain reimbursement. This time around, the omens are different, given the inadequacies of current treatments for fistulizing Crohn's disease.

Alofisel's approval also marks the maturation of allogeneic stem cell therapy, a technology that promises off-the-shelf convenience, but which has, so far, failed to make a substantial impact across a range of conditions (**Table 1**). Prochymal (remestemcel-L), another mesenchymal stem cell therapy, was the early standard bearer. Its developer Osiris Therapeutics, of Columbia, Maryland, gained approvals in 2012 in Canada and New Zealand for treating acute graft-versus-host disease in pediatric bone marrow transplant patients, despite two negative phase 3 trials. But the product was a commercial failure, and Mesoblast acquired the Osiris stem cell business and associated IP shortly afterwards (*Nat. Biotechnol.* **31**, 1061, 2013).

That deal to acquire the IP has started to pay off for Mesoblast. The agreement with TiGenix sends a clear message to other firms in the same space. "There are a number of other companies developing mesenchymal stem cell therapies, which we consider are infringing [our patents]," says Mesoblast CEO Silviu Itescu. The agreement with TiGenix, he says, may be the first IP licensing deal involving a commercial stem cell therapy product. "Quite frankly, without a license from us they would not have been able to launch their product," he says. Mesoblast's own clinical pipeline of therapies includes an updated version of Prochymal, MSC-100-IV, which is now nearing a phase 3 read-out. "We took it on and optimized it and we initiated a whole new manufacturing process in Singapore. This is a new product," he says. Mesoblast's Japanese licensee JCR Pharmaceuticals, of Ashiya, markets a version of the product as Temcell HS. Mesoblast is also close to a read-out from a phase 3 trial of its congestive heart failure therapy MPC-150-IM, which is based on its newer mesenchymal progenitor cell (MPC) technology. MPCs, says Itescu, are far more potent immunomodulators than MSCs and represent the company's long-term future. They are in the same cell lineage as, but are upstream from, MSCs and can be isolated using antibodies directed against cell surface markers, such as stromal precursor

Table 1 Selected allogeneic stem cell therapies

Company	Therapy	Composition	Indication	Status
JCR Pharmaceuticals, Mesoblast	Temcell HS	Allogeneic MSC therapy	Acute graft- versus-host disease in bone marrow transplant patients	Approved in Japan 9/2/2015
Stempeutics (Bangalore, India)	Stempeucel	Ex vivo cultured adult allogeneic MSCs	Critical limb ischemia due to Buerger's disease	Approved in India 5/30/2016
TiGenix, Takeda	Alofisel (darvadstrocel; Cx601)	Allogeneic expanded adipose-derived MSCs	Complex perianal fistulas in adult Crohn's disease patients	Received CHMP positive opinion on 12/15/2017; global phase 3 trial ongoing
Mesoblast	MPC-150-IM	Allogeneic MSCs	Congestive heart failure	Phase 3
Mesoblast	MSC-100-IV	Allogeneic MSCs	Acute graft- versus-host disease	Phase 3
Pluristem Therapeutics (Haifa, Israel)	PLX-PAD	Placenta-derived, mesenchymal-like, adherent stromal cells	Critical limb ischemia	Phase 3
SanBio (Tokyo) Sunovion Pharmaceuticals (Marlborough, Massachusetts)	SB623	Adult bone-marrow-derived cells transiently transfected with a plasmid encoding the intracellular domain of human Notch-1	Chronic motor deficit due to ischemic stroke	Phase 2b
Anterogen (Seoul)	Allo-ASC-DFU	Hydrogel sheet containing allogeneic adipose-derived MSCs	Burn injury	Phase 2
Bone Therapeutics (Gosselies, Belgium)	Allob	Allogeneic osteoblast cell therapy derived from ex vivo-cultured bone marrow cells	Adjunct to spinal fusion surgery	Phase 2
Capricor (Beverly Hills, California)	CAP-1002	Allogeneic cardiosphere-derived cell therapy containing cardiac progenitor cells	Duchenne muscular dystrophy	Phase 2 planned in 2018
Promethera Biosciences (Mont-Saint-Guibert, Belgium)	HepaStem	Liver-derived MSCs	Acute-on-chronic liver failure	Phase 2
ReNeuron (Bridgend, Wales)	CTX	Allogeneic neural stem cell therapy	Stroke disability	Phase 2

Source: Clinicaltrials.gov, PubMed, FDA.gov, company websites

"A bull is a lot better at doing it [procreating] than we are, and he enjoys it a lot more," Alison Van Eenennaam, of UC Davis, comments on gene editing techniques to create a CRISPR-edited bull that will sire only males, which are more commercially valuable to ranchers for their size. It's possible to do this through artificial insemination, but Van Eenennaam's approach [of creating females that harbor the *SRY* (testis-determining factor) gene on its X chromosome] enables the process to go on by natural reproduction. (*MIT Technology Review,* 10 January 2018)

"You'll take the call because you've got a friendly relationship. You'll take the call because these people are going to help you in your future career [and] get you a job making three times as much." Diana Zuckerman, president of the nonprofit National Center for Health Research and a former congressional staffer, comments on the appointment of a former Lilly executive, Alex Azar, as head of Health and Human Services, one of over a dozen such appointments to industry insiders, and how it raises the specter of influence peddling. (*STAT* 25 January 2018)

antigen 1 (STRO-1). But the maturation of MSC-based therapies still offers immediate revenue opportunities given Mesoblast's blocking IP in this area.

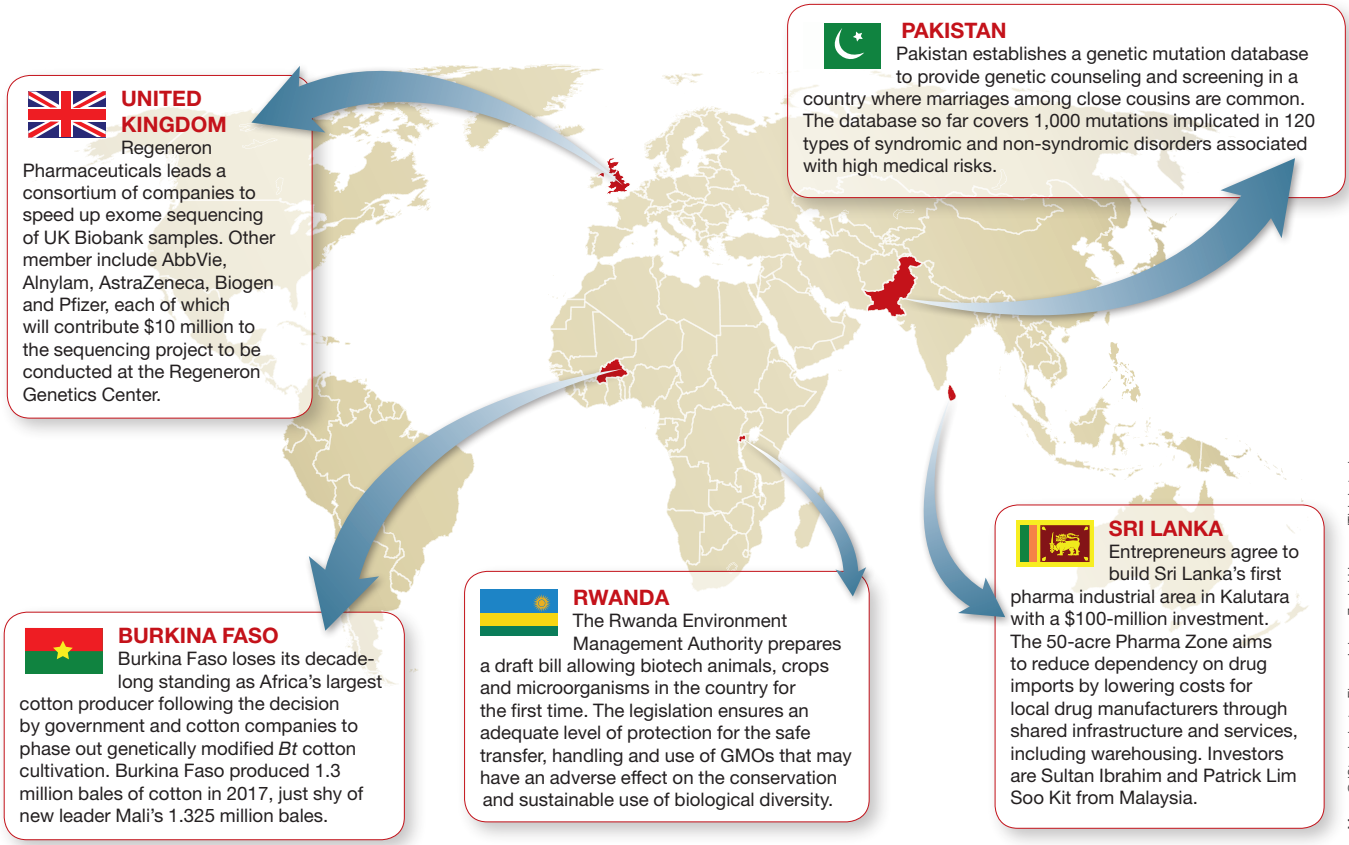
Notwithstanding the current regulatory progress, the wider field of mesenchymal stem cell biology remains controversial. Some critics, indeed, have called for the very term to be abandoned. "The term mesenchymal stem cell is jargon. It means so many different things," says Pamela Robey, acting scientific director of the stem cell unit at the NIH, and chief of the matrix metalloproteinase section, craniofacial and skeletal diseases branch of the National Institute of Dental and Craniofacial Research. What are loosely termed MSCs do not have a common embryonic origin and do not constitute a single lineage but are stem cells or progenitor cells with fibroblast-like cell-surface features, which can originate in a range of tissues (*F1000Res.* **6**, 524, 2017). "The rationale for using these cells for what we call the paracrine effect is very slim," Robey says. Drug regulators are not being rigorous enough, she says, in examining in a detailed fashion the immunomodulatory and anti-inflammatory effects claimed on their behalf. "In their defense, this is a newly emerging area," she says. In February, the FDA entered a collaboration with Cytobank of Santa Clara, California to develop machine learning-driven methods to classify MSCs preparations aimed at improving cellular manufacturing. Regulators are, however, under pressure from the public, as well as from industry, not to block innovation in the field. "They're walking a tightrope, so I can't really blame them." The future commercial—and clinical performance—of Alofisel will offer a good gauge of the EMA's ability to strike the correct balance.

Cormac Sheridan

CORRECTION

In the February 2018 issue, in the News Analysis "California voters and CIRM—will lightning strike twice?", the statement that CIRM's Transition Committee "considered requesting $5 billion (or a total of $10 billion) from the electorate" should have read the "Committee heard a presentation for another $5-billion ($1-billion with interest) citizen-sponsored proposition." The errors have been corrected in the HTML and PDF versions of the article on 22 February 2018.

Around the world in a month



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