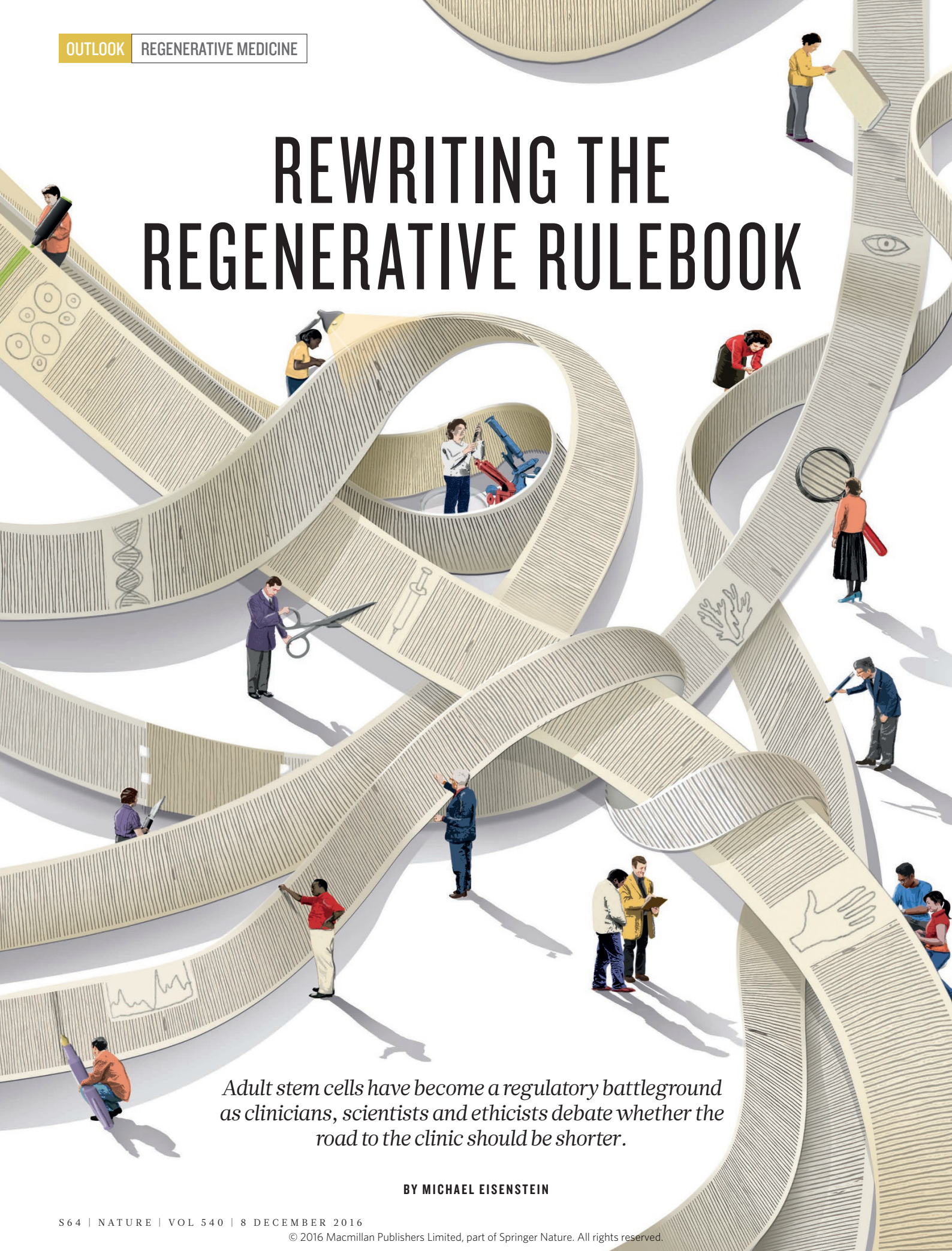
REWRITING THE REGENERATIVE RULEBOOK



Adult stem cells have become a regulatory battleground as clinicians, scientists and ethicists debate whether the road to the clinic should be shorter.

BY MICHAEL EISENSTEIN

Shortly after Paul Knoepfler started his blog, e-mails began to flood his inbox. In 2010, his was one of few websites focused on making stem-cell science accessible to the public, and numerous people came looking for answers.

Knoepfler, a stem-cell biologist at the University of California, Davis, was well-versed in the scientific state of the field, but the inquiries he received took him aback. "They weren't really asking about academic clinical trials," he recalls. "They were almost all asking about stem-cell clinics." He realized that people were desperate for information on the facilities that offered stem-cell preparations (which were often poorly defined) for an array of medical conditions, including many for which no medical benefits have been proved, such as autism spectrum disorder and Parkinson's disease. At the time, these shadowy operations were based mainly in Asia, Latin America, Eastern Europe and the Caribbean, outside the reach of the US Food and Drug Administration (FDA) and the European Medicines Agency.

Today, the US stem-cell business is booming, and the FDA has a fight on its hands. In a recent study, Knoepfler and Leigh Turner, a bioethicist at the University of Minnesota in Minneapolis, counted 351 US-based businesses running 570 clinics that offer stem-cell treatments for cosmetic, orthopaedic, neurological and other conditions (L. Turner & P. Knoepfler *Cell Stem Cell* **19,** 154–157; 2016). The FDA has taken a hard line in its approach to stem-cell therapies, with regulations that generally call for the same rigorous testing procedures currently required for drugs and devices, but has done little to stave off the growth of the stem-cell-clinic industry. Meanwhile, some doctors and patients are pushing back, arguing that the agency is preventing medical progress with its overly strict and cautious approach to stem-cell regulation and impeding physicians' right to practise medicine as they see fit.

The lines are now being drawn. Critics of the current regulations are challenging the fundamental aspects of stem-cell-therapy oversight and pursuing legislative solutions, whereas defenders of those rules favour a more conservative approach. "There's this difficult-to-define 'no man's land' between what is clearly the practice of medicine and what clearly isn't," says Charles Cox, a paediatric surgeon working in regenerative medicine at the University of Texas Health Science Center at Houston. "That's where the tension arises."

ADULT MATERIAL

The current dispute centres on a class of adult (as opposed to embryonic) stem cells that can be easily harvested and prepared for transplantation through a minor surgical procedure. These mesenchymal stem cells (MSCs) can be collected from a patient's bone marrow or fat tissue, or from donor tissues, including the placenta and umbilical cord. MSCs have the capacity to form fat, bone or cartilage, making them potentially useful for repairing bones and joints. They also churn out biomolecules that can quell inflammation and stimulate repair in various tissues of the body. "It's more than just bone regeneration — for example, we're also spanning to neurological indications and autoimmune diseases," says Massimo Dominici, who studies clinical applications of MSCs at the University of Modena and Reggio Emilia in Italy.

The accessibility and physiological properties of MSCs have made them the cell of choice for most clinics, but many of the ways in which these cells are used run afoul of FDA rules. Agency regulations establish two broad categories for what it terms human cells, tissues and cellular and tissue-based products (HCT/Ps). Products that fall under a part of the rule known as section 361 are essentially treated like donor blood and organs. These regulations emphasize protecting recipients against transmission of infectious disease, but do not require extensive agency oversight.

Other HCT/Ps are governed by section 351. These are considered indistinguishable from drugs and must undergo a rigorous regulatory process before being given to patients. Some of the lines that separate section 351 products from those of section 361 are clearly drawn. For example, cells and tissues used homologously, meaning they perform the same function in the recipient as they do in the donor — such as the transplantation of bone marrow to restore healthy blood-cell production — are regulated under section 361. And therapies that employ a patient's own stem cells (autologous) are more likely to fall under section 361 than those that use allogeneic cells from a donor. The situation becomes murkier in other areas. Any tissue that is more than 'minimally manipulated' is viewed as a drug. Ambiguities can arise, however, because separating stem cells from their neighbours always entails some degree of manipulation. "Sometimes you have to use enzymes to digest tissue and isolate the MSC precursors," says Dominici. "In the past, this was considered minimal manipulation, but now the trend is to consider it a non-minimally manipulated procedure."

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The FDA's authority over MSCs was tested in a high-profile lawsuit against Regenerative Sciences in Broomfield, Colorado. The treatment sold by the firm used autologous bone-marrow-derived MSCs to repair joint injuries. This is a plausible application for these cells, but the cells were being cultivated at a separate laboratory before re-implantation at the clinic. The FDA said that this represented more than minimal manipulation, and in 2014, the US Court of Appeals upheld the agency's right to regulate the treatment. Many biologists agree with this interpretation of the regulations. "Cell division in culture is nothing like when cells divide in the body," says Lynn O'Donnell, a cell-therapy specialist at Ohio State University's Wexner Medical Center in Columbus. "You're accelerating the process, which can lead to increased risk for potential genetic alterations."

RETICENT REGULATORS

Despite the court supporting the FDA's interpretation of the regulations, the agency has not pursued legal action against any more stem-cell clinics. This has surprised many researchers who were expecting to see an increase in regulatory activity, says Turner. "That does not appear to have happened," he says.

The FDA declined to comment for this article, but did issue a statement asserting its authority to respond to abuses of HCT/P regulations with "a variety of advisory, administrative and judicial actions depending on the particular violations". These actions have generally taken the form of warning letters, which threaten further action if violations are not addressed. However, only a handful of letters have been issued to clinics, with no clear pattern. Turner notes that one recent letter targeted a clinic that offered only minor cosmetic procedures, while other businesses that make more ambitious medical claims continue to operate unimpeded.

Some doctors, however, think that they are being unfairly constrained. Ricardo Rodriguez is a cosmetic surgeon in Baltimore who heads the International Federation for Adipose Therapeutics and Science (IFATS), an organization that promotes research of therapies based on fat-derived

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cells. He thinks that the FDA's position is grounded in excessive caution, motivated, in part, by past experiences in gene therapy — including when the death of a trial participant stalled clinical development for more than a decade. "The FDA made these arbitrary rulings many years ago that have very little to do with science and a lot to do with past experience and high-profile disasters," says Rodriguez. He feels that the FDA regulations are overly broad and simplistic, denying physicians access to relatively safe therapeutic strategies by lumping them together with higher-risk regenerative-medicine approaches.

SETTING BOUNDARIES

During 2014 and 2015, the FDA issued four draft guidance documents detailing its interpretation of the HCT/P regulations, but these did not provide the level of clarity that many researchers and clinicians were hoping for. "I can wade through them for the most part, because I've been reading FDA stuff for years," says Knoepfler. "But they're not simple — they're complicated, and not concrete."

These documents have also stirred debate about fat-derived stem cells. This subpopulation of MSCs was identified in 2001, and are not referred to specifically in the original HCT/P regulations, which were issued the same year. However, these cells have since generated intense clinical interest — either in a purified form or as a heterogeneous, MSC-enriched preparation of fat known as the stromal vascular fraction. The FDA's draft guidance on adipose tissue brings these various formulations under a common umbrella, but critics argue that the agency's interpretation of this tissue is too narrow. "They are defining adipose tissue as solely structural — meaning that it cushions and supports, and that's all it does in the human body," says Mary Ann Chirba, a legal scholar who specializes in health policy at Boston College Law School in Newton, Massachusetts. The draft guidance defines even a fat transplant to the breast for augmentation or postsurgical reconstruction purposes as non-homologous, on the premise that the biological purpose of the breast is milk production — something that is beyond the remit of adipose tissue. In Rodriguez's view, the FDA's definition of fat's physiological role "has no basis in biological reality", and overlooks fat's broader endocrine, metabolic and other functions.

Stem cells are prepared before being given to a patient at a clinic in Mexico.

XINHUA/ALAMY

However, Knoepfler points out that most approaches for producing adipose MSCs — and particularly the stromal vascular fraction preparations commonly used in clinics — yield mixtures of cell types in addition to the desired stem cells that bear little resemblance to natural fat. These are, therefore, sufficiently manipulated to trigger stricter regulation regardless of how they are used. "I'm on the same page as the FDA in thinking that this is something that is not a natural product," he says. However, Knoepfler also expresses some concern about the narrowness of the FDA's biological definitions. "I do not agree with their position on breast reconstruction," he says.

Even with purified MSCs, questions remain about exactly what they are and how they work. Indeed, the biologist who coined the name mesenchymal stem cell in 1990 — Arnold Caplan, now at Case Western Reserve University in Cleveland, Ohio — has come to regret the term. "When I lecture, I beg the audience not to call them stem cells," he says. Caplan points to evidence that MSCs are derived from precursor cells that surround blood vessels all over the body, where they stimulate local tissue repair when damage or disease occurs, rather than rebuilding the tissue themselves — the main feature associated with conventional stem cells. Because MSCs are active in myriad tissues and organs, Caplan views them through a different lens. "Based on what these cells do *in vivo*, I'd say you've got homologous use for MSCs in any tissue where you have a blood vessel," he says.

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Dominici's experience of using MSCs for bone regeneration has led him to a different conclusion. "Not all MSCs are capable of doing what we want them to do," he says. MSCs derived from one tissue may exert different effects when transplanted into another part of the body, he says. Dominici thinks that a better way forward is to develop molecular assays to profile the therapeutic activity of different MSC preparations. This information could be more useful to clinicians in determining which cells are appropriate for a given disease than where the cells initially came from.

CONFLICT RESOLUTION

In September, the arguments about the FDA's oversight of stem-cell therapies were aired at a two-day hearing, at which speakers from almost every sector with a stake in stem cells discussed the draft guidances. Chirba was among those advocating for a reconsideration of homologous-use rules. "Most FDA regulatory frameworks evaluate devices and drugs based on intended use and the intention of the person who is applying it," she says. "I don't understand why you can't look at a cell or tissue the same way." Many patients related personal tales of recovery and pleaded for easier access to the treatments that they saw as the source of their relief. Other speakers offered words of caution, including cell biologist Jeanne Loring of the Scripps Research Institute in La Jolla, California, who warned that "a lack of understanding or deliberate ignorance of regulations has led to increasing exploitation of desperate patients by incompetent clinics".

The FDA may respond to issues raised at this hearing, but it is under no obligation to do so. Caplan believes that little will change. "The only way to advance this field is by passing legislation," he says. Caplan helped formulate the REGROW Act, a bill to accelerate the entry of section-351-regulated cell and tissue therapies into the market. In its first iteration, the bill would have conferred conditional approval to HCT/Ps that demonstrated clinical safety and some data supporting efficacy — essentially eliminating phase III trials. Phase III testing is intended to provide robust proof of efficacy, but is also labour-intensive and expensive: one study estimates that costs range from US$11.5 million to $52.9 million (A. Sertkaya *et al. Clin. Trials* **13,** 117–126; 2016), depending on the field, and this is likely to be higher for a cutting-edge cellular therapy.

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A protest in Rome in support of the controversial Stamina Foundation, which claimed that its stem cells could treat diseases such as Parkinson's.

Supporters of the bill think that it would level the playing field for companies and clinical researchers that lack the resources of big pharmaceutical companies. Japan adopted such a regulatory approach in 2014, and although too little time has passed to determine its pros and cons, Caplan says that "all our American companies have now set up shop in Japan". However, Cox feels that the costs and bureaucratic hurdles have not thwarted his research team's clinical efforts, and does not see these hurdles as an impediment to the growth of the field. "Some of it is a bit of a pain, but that hasn't been a barrier," he says. "It's only a barrier if you don't want to keep records and do things in a rigorous way."

Japan requires post-market surveillance to prove safety and efficacy within a defined window of time, as a prelude to permanent approval, and this was an initial component of REGROW as well. However, the bill has divided patient advocates, with some applauding the idea while others remain wary of moving too quickly. "This could create a situation where patients and providers are paying for a product that's not proven to be safe or effective," says Bruce Bebo, executive vice-president for research at the National Multiple Sclerosis Society in New York City. "It lowers standards, and I think it would disincentivize more-rigorous research." The bill was also opposed by the Alliance for Regenerative Medicine, a cell-therapy industry group in Washington DC, and the most recent version of it has abandoned conditional early approval to focus on more conventional strategies for accelerating clinical trials. The bill is still in committee, and may be further modified before coming up for a vote.

Both the European Union and the United States have compassionate-use exemptions that can give people with severe and untreatable diseases access to drugs in the clinical pipeline. Many stem-cell researchers support this loophole, but there are opportunities for abuse. For example, in 2013, Italy was rocked by a scandal surrounding a Brescia-based company called the Stamina Foundation, which used a controversial trial to deliver unproven MSC-based treatments to people with incurable diseases such as Parkinson's and muscular dystrophy. "Patients were misled by false information regarding the potential of these cells," says Dominici, who presented evidence against Stamina to the Italian Senate.

Data suggest that MSC-based therapies are generally safe when applied under controlled clinical conditions. However, adverse events and even deaths have been reported after patients have visited stem-cell clinics, and these will inevitably become more regular as more people visit them. "One thing about medicine is that we should never underestimate our ability to make things worse," says Cox. Indeed, one physician recently reported treating three women who became blind after receiving adipose-derived MSCs as a treatment for macular degeneration in a Florida-based clinic (H. Ledford *Nature* **537,** 148; 2016). But as Knoepfler discovered, convincing patients — particularly those with chronic or terminal disease — to wait for the science to advance, is a hard sell, and it has become clear that researchers and regulators need to do a better job of building bridges so that patients start perceiving regulatory agencies as allies rather than obstructions.

Research societies such as the International Society for Cellular Therapy in Vancouver, Canada, and the International Society for Stem Cell Research in Skokie, Illinois, are stepping up by providing educational materials to steer people away from clinics offering unproven treatments. However, without a concerted effort from regulators, this battle might be won by the slickest marketing — an area where commercial clinics have an edge. "A buyer beware mentality," says Turner, "doesn't do much to shield people from the most disturbing part of the marketplace." ■

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