FDA snubs first smart pill

Proteus Digital Health

The US Food and Drug Administration (FDA) has rejected an application from Proteus Digital Health and partner Otsuka for a prescription medication embedded within a monitoring device. The product is a forerunner among a growing health trend for digital self-monitoring (*Nat. Biotechnol.* **32**, 965–966, 2014): a single table combines an ingestible sensor made by Redwood City, California–based Proteus with Tokyo-based Otsuka's antipsychotic Abilify (aripiprazole). The wireless sensor–drug combination tracks when pills are taken and can collect information on patients' physiological responses to help boost adherence and allow treatments to be tailored to the individual. The sensor in the tablet transmits information to a wearable sensor patch, and the data are collected by a medical software application and transmitted to the patient or, with the patient's consent, to clinicians, friends and family (*Nat. Biotechnol.* **34**, 15–18, 2016). Although the Proteus technology has already been cleared in the US and Europe for use in conjunction with existing medicines—though not as a device embedded in a tablet, as in this case—the FDA issued a complete response letter to the Tokyo-based Otsuka and the Redwood City, California–based Proteus in April. The agency is now seeking further confirmation on the sensor–drug combination's performance under the specific conditions in which it is likely to be used, as well as further risk evaluations for users. Abilify is an atypical antipsychotic, and the submitted application was for the device–pill to treat schizophrenia and episodes related to bipolar disorder and as an adjunct treatment for major depression.

"We already have quite a lot of experience in the last 10 years working with multidimensional data. If you look at how much of that has moved to clinical application, it's close to nil." John Ioannidis, of Stanford University, comments on the relatively small scale of Google's life science company Verily and its Baseline Project, which is collecting data from 10,000 people. (*STAT*, 6 June 2016)

Group, purchased millions of dollars' worth of shares. At the time Trounson joined the board, StemCells landed $20 million from two investors, which was key to funding the company's operations in 2015. The company's stock offering earlier this year raised $8 million, and less than a month before going out of business, StemCells announced its intention to free up shares for another offering.

During almost two decades, the biotech put the HuCNS-SC line to the test in a wide variety of early-stage clinical studies. Indications included geographic atrophy of age-related macular degeneration (AMD), connatal Pelizaeus-Merzbacher disease (PMD), and infantile and late infantile neuronal ceroid lipofuscinosis (specifically Batten disease). Neither these nor the spinal cord injury trials turned up safety concerns, but they showed little in the way of efficacy. Many of the company's results revealed biological activity worthy of further research, but none gave the company justification for further product development.

Without funds to continue, there's no way to know whether it was the cells or something about the trial design that failed, says Irving Weissman, director of the Institute of Stem Cell Biology and Regenerative Medicine at Stanford University and a StemCells cofounder and board member, speaking in a personal capacity, not as a company representative. Weissman is working to ensure that the cells become available for research in academia, he says. "I hope where the cells land next is with groups that have the funds to learn what went wrong in this trial," he says. "This type of research needs both bench-to-bedside, and, here, bedside-to-bench, research."

No neural stem cell trial by any company to date has been justified by the preclinical data, says Scott Whittemore, director of the Kentucky Spinal Cord Injury Research Center and director of the Interdisciplinary Program in Translational Neuroscience at the University of Louisville School of Medicine. Most importantly, none of the preclinical data has been independently replicated in other laboratories, he says. Currently, there is no consensus on the criteria needed to move from animal studies to human trials in these cases, he says.

Understanding the underlying mechanisms is important for predicting how engrafted cells will affect functional recovery, says Whittemore. Some of the observed biological activity in clinical trials was due to a poorly understood mechanism by which the engrafted cells engendered a host reparative response, rather than due to cell-specific effects, he says. "The mechanism by which any kind of recovery occurred was very unclear."

StemCells' failure could stoke concerns about the future of cellular therapies and regenerative medicine among investors and the California public, but some biotech industry insiders are taking a more sanguine view. Carpenter, who was in charge of the neural stem cell program at CytoMx and worked on Geron's stem cell program early on, noted that investors are likely to face reduced risk going forward. Acquisitions and spinouts are occurring with more mature technologies, Carpenter says. "The paradigm is very much different than it was back when StemCells launched or when Geron acquired the early human ES [embryonic stem cell] technologies," she said.

Early stem cell therapies belong in academia through phase 1/2 trials, says Weissman. The academics who understand the biology of stem cells and regenerative medicine must stay centrally engaged through early-phase clinical trials, he says. "That kind of long-term direct involvement of all relevant parties in the process from discovery to registered therapy is rare in companies." Getting a neural stem cell therapy for spinal cord injury through clinical trials is among the most challenging problems in biotech. "Neural stem cell transplantation is a provocative intervention," says Stephen Huhn, StemCells' chief medical officer and vice president of clinical research, because such therapies are unproven in any context, and there are no approved treatments to act as a benchmark. "The paradigm here is to explore patients who are at the worst end of the scale, not at the moderate or better end of the scale where perhaps the cellular therapy might have a better chance of showing efficacy," he says.

The fundamental problem with stem cell CNS therapies is that there isn't much ongoing stem cell activity or migration after transplantation into the brain, says Mahendra Rao, founder and CEO of Novato, California–based NxCell and vice president of regenerative medicine at the New York Stem Cell Foundation. Many companies bet otherwise, he says. "So they rushed in with the wrong assumptions, which unfortunately did not pan out."

StemCells tried to do too many things and conduct too many trials for different indications, Rao says. Each trial costs $15 to $30 million, and if the results are unimpressive then "the writing is on the wall," he says.

StemCells' failure is going to slow down the field, says Enal Razvi, managing director of the US subsidiary of life-sciences market research, consultancy and conference producer Select Biosciences, located in Sudbury, UK. "And I think it's for the best, because this needs to happen," he said. "I think the companies are getting too far ahead of themselves."

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