Verily chases a perfectly healthy human

Google startup Verily Life Sciences is expecting 10,000 people to sign up for a four-year study to find out why healthy people transition from health to illness. Verily, located in Mountain View, California, is partnering with Duke University and Stanford Medicine to enroll participants from different backgrounds in the next few months. The Project Baseline study will collect data from participants wearing the Study Watch (Verily's investigational device, available only for research purposes). The watch features sensors for "unobtrusive biosensing," says Verily in a blog post, to measure vitals such as heart rate, ECG, electrodermal activity, as well as movement. Biospecimen samples, imaging, surveys and clinical visits will also be used to develop a reference, or a 'baseline', for wellness. Verily will also use the Study Watch in the Personalized Parkinson's Project, an observational study to identify patterns of progression in this disease. The pioneer in digital data gathering outside the clinical setting was Apple with its ResearchKit. This software tool works as an iPhone app feeds data directly to medical researchers as individuals go about their daily lives. Apple launched ResearchKit to encourage the millions of iPhone users to participate in clinical research studies (*Nat. Biotechnol.* **33**, 322, 2015). Verily already has several partnerships with large pharma, and works with Paris-based Sanofi on devices for type 2 diabetes management, with GlaxoSmithKline on miniaturized electronic devices for peripheral nerve simulation (*Nat. Biotechnol.* **34**, 904–908, 2016), with Johnson & Johnson on surgical robotics and with Novartis for glucose-checking contact lenses.

"I'm starting to hear more and more that we are better than I think we really are. We're starting to believe our own bullshit." Otis Brawley, chief medical officer at the American Cancer Society, points out that the hype that often surrounds new cancer therapies generates false hope. (*CNN,* 26 April 2017)

"There's [sic] all kinds of elephants, and the room is crowded with them, I suppose, but that one didn't get much attention." NIH director Francis Collins comments on the failure to discuss drug pricing during a meeting held at the White House between biopharma executives and President Donald Trump's daughter and son-in-law, despite previous critical remarks by the US president on the subject. (*CNBC,* 8 May 2017)

"That's the million-dollar question: What's the right amount? What's the appropriate level of safety concerns to have identified only once the product is out of the gate?" Caleb Alexander, co-director of the Johns Hopkins Center for Drug Safety and Effectiveness, points at a study from Yale researcher Joseph Ross showing that nearly one-third of approved drugs have safety issues. (*STAT,* 9 May 2017)

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Nobel Prize–winning stem cell researcher Shinya Yamanaka.

present in the adult brain. "Those neurons know exactly where to go."

Frequency's lead program arose from the research of Langer and his longstanding collaborator Jeffrey Karp, associate professor at Brigham and Women's Hospital and Harvard Medical School, in Boston. Together with researchers at the Hubrecht Institute for Developmental Biology and Stem Cell Research, Utrecht Medical Center, Utrecht, the Netherlands, they initially developed a novel technique for cultivating intestinal LGR5-expressing cells on a large scale (*Nat. Methods* **11**, 106–112, 2014). LGR5$^+$ cells are key to the ability of the intestinal epithelium to regenerate itself every four to five days. "It will keep forming new tissue until you're 100 years old—for your whole life," says Loose. Although LGR5$^+$ cells are also present in the cochlea, the same regenerative capacity is absent. Damage to the hair cells, which transduce the vibrational energy of sound into an electrical signal that can be transmitted to the brain, is a major cause of hearing loss. The new cultivation method enabled Langer and Karp's group to experiment with different conditions to direct the differentiation of LGR5$^+$ cells along various lineages.

More recently, Karp, Langer and collaborator Albert Edge, professor of otolaryngology at Harvard Medical School, reported that a combination of Wnt activation with a Gsk3-β inhibitor and alternate rounds of Notch activation and inhibition, with a histone deacetylase inhibitor and a gamma secretase inhibitor, respectively, caused murine cochlear supporting cells to differentiate into LGR5-expressing progenitor cells, which gave rise to hair cells that were anatomically and genetically similar to their naturally occurring counterparts (*Cell Rep.* **18**, 1917–1929, 2017).

The biological findings are not new, but the efficiency of the reprogramming system is a considerable advance on previous efforts. Frequency is using this work as a foundation for its internal pathway discovery efforts—the reprogramming cues it will probably deploy will differ from those that Langer and Karp employed. The effort is already quite advanced. "Within the next year we expect to be in the clinic," says co-founder and CEO David Lucchino. The company also plans to apply the same basic principle to other cell types in other settings, such as skin disorders, muscle regeneration and gastrointestinal disease.

UCSF's Ding is one of the co-founders of Tenaya Therapeutics, a Gladstone Institute spin-out, which last year raised $50 million in series A funding to develop regenerative therapies for heart failure. One of its programs is based on a protocol to nudge cardiac fibroblasts to differentiate into induced cardiomyocyte-like cells, which can regenerate functioning heart tissue. Ding and collaborators recently reported that adding a Wnt inhibitor and a Tgf-β inhibitor to an existing protocol, based on three transcription factors, Gata4, Mef2c and Tbx5, improved its efficiency about eightfold, while also accelerating the process (*Circulation* **135**, 978–995, 2017). As currently constituted, however, the putative therapy is an unwieldy proposition. "We're further optimizing and formulating what would be the clinical candidate," Ding says. He is also involved in a collaboration with Thomas Reh, of the University of Washington School of Medicine, in Seattle, the aim of which is to reprogram rod photoreceptors, which mediate night vision, to cones, which are responsible for central vision and color perception. This approach could help to reduce or delay the effects of retinitis pigmentosa, an autosomal dominant degenerative condition that initially affects rods. They have identified a small molecule, photoregulin 1 (Pr1), which acts on the nuclear hormone receptor Nr2e3, a key regulator of rod gene expression (*Invest. Ophthalmol. Vis. Sci.* **57**, 6407–6415, 2016). Its deletion leads to the reprogramming of rods into cells that resemble cones; Pr1 appears to slow rod degeneration. "We're going to start a new company based on that [research]," Ding says.

The attractions of *in vivo* reprogramming lie in its potential to engender therapeutic effects that are on a par with gene or cell therapy, without any of the attendant risks associated with those modalities. Progress has been necessarily slow, given the complexities involved in developing a comprehensive understanding of how drug leads influence the cell biology and molecular biology of healthy and diseased tissues. The present flow of investment funds should at least help to accelerate the efforts that are now underway. "Everything in medicine—the journey from discovery to clinical implementation—just takes a long time. There's fits and starts," says Langer.

Cormac Sheridan *Dublin*