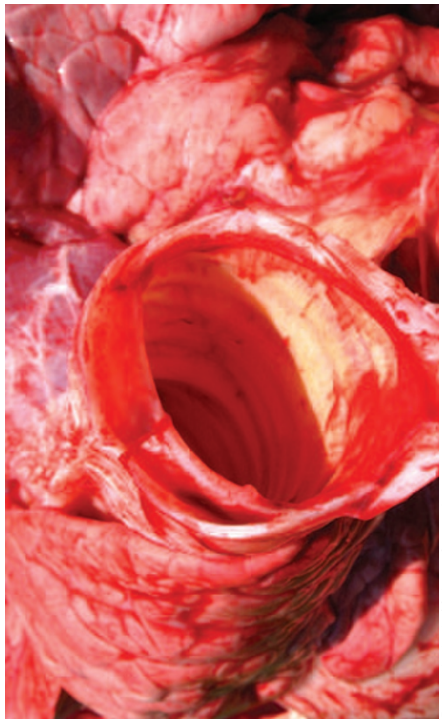
Engineered tracheas, corneas and arteries enter clinical testing

The first human recipient of a bioengineered replacement trachea is still alive and well five years later. In February, after discussion with the US Food & Drug Administration (FDA), Harvard Bioscience spinout Harvard Apparatus Regenerative Technology (HART) of Holliston, Massachusetts, announced that it is preparing to launch a multisite, phase 1 study of bioengineered tracheas in the US and Europe, with the goal of reaching the market in 2017. Several other tissue-engineering companies are making similar forays into clinical testing, sparking hopes for renewed vigor in a sector recently hit by Shire's decision to dispose of its Dermagraft franchise (**Box 1**).

Organogenesis was one of the first companies to make commercial headway in the area of cell-based regenerative therapeutics, winning FDA approval in 1998 for Apligraf, and more recently for Gintuit. Although cell-based, these patches to repair skin and gum, respectively, actually turn out be a temporary presence that ultimately disappears from the recipient's body. "If you take a biopsy of the wound after about four to six weeks, you will not find any residual Apligraf," says Organogenesis CEO Geoff MacKay. "It's a temporary biological stimulus that induces the patient to heal themselves." Wound healing remains one of the most active sectors of the industry (*Tissue Eng. Part B Rev.* **18**, 155–166, 2012).

Off-the-shelf products typically use donor allogeneic cells and generally appear to be nonimmunogenic. But in tissue reconstruction, autologous cells derived directly from the patient are seen as preferable. Sanofi's MACI (matrix-induced autologous chondrocyte implant), a product to treat cartilage defects, consists of a collagen scaffold fashioned from an individual's own cartilage-forming chondrocytes, seeded onto a supportive pig collagen membrane, which is then surgically applied to the joint. It is currently commercially available in Europe and Asia but not the US.

An appropriately shaped matrix may sometimes be enough to induce repair by the patient's own cells. Several companies currently market cell-free grafts for bone and joint repair. The regulatory journey is also likely to be easier without cells. May Griffith and colleagues at Linköping University in Sweden began seeding corneal cells onto a molded collagen surface, but her team subsequently moved to a matrix-only approach to formulate corneal implants. "If I grow cells on top of a matrix, it becomes an advanced therapy and medicinal product in the EU, which is a lot more difficult to get through the regulatory agencies," she says. Griffith is embarking on a three-site clinical trial in Europe to test biosynthetic corneas made from recombinant human collagen–phosphorylcholine hydrogels as corneal substitutes. Patients who received first-generation implants in a phase 1 trial four years ago showed robust signs of corneal regrowth and partial recovery of vision (*Biomaterials* **35**, 2420–2427, 2014), with only one case of rejection—suggesting a potentially safe alternative to a limited supply of donor tissue.



Ramon Andrade / Science Source Images

Tracheas grown in bioreactors have been successfully implanted.

Complex organs require more crafting. As in the successful synthetic trachea transplants grown in HART's 'InBreath' bioreactor, replacement tissues can be produced by incubating cells with three-dimensional (3-D) scaffolds in bioreactors, under conditions that recapitulate physiological conditions. Among the most popular strategies for tissue reconstruction are 'decellularization-recellularization' (decell-recell) methods that involve stripping living cells from an organ or piece of tissue, leaving behind only the framework of extracellular matrix (ECM) proteins that supported those cells and still retain the shape of the source

IN brief

Circadian rhythm drug approved

The US Food and Drug Administration (FDA) in January approved Vanda Pharmaceuticals' Hetlioz (tasimelteon), the first drug to treat non-24 sleep-wake disorder. The condition, known as non-24, is common in totally blind people with no light perception, who lack the environmental cues to synchronize their endogenous circadian rhythm with the day-night cycle. Hetlioz is a small-molecule agonist for type 1 and 2 melatonin receptors, known to play a key role in regulating circadian rhythms. Off-the-shelf melatonin (*N*-acetyl-*5*-methoxytryptamine) formulations are sold as food supplements in the US, claiming to promote sleep and ease jet lag. They have also been used to treat non-24. But dosage of these melatonin preparations varies widely, and efficacy is unreliable. In addition, no clinical trials have tested melatonin's efficacy in non-24. Phase 3 study results with Hetlioz show that if taken once daily at the same time before bedtime, the drug improves sleep-wake parameters, such as total sleep time and timing of sleep. Non-24, which can cause disrupted sleep-wake patterns and excessive daytime sleepiness, affects 80,000–100,000 people in the US. Morningstar, a Chicago-based independent investment research company, estimates $600-million peak sales for Hetlioz. "We assume that it's going to be a slow wrap-up," says Morningstar analyst Stefan Quenneville, "which [comes] down to two main reasons: Vanda is a small biotech without the marketing heft behind them and non-24 is a relatively new indication." Vanda, located in Washington, DC, has launched an active outreach program to increase awareness of non-24, and commercial launch is slated for the second quarter of this year. *Man Tsuey Tse*

IN their words

"[Sovaldi] is the poster child for everything that is wrong with drug prices." Michael Weinstein, president of the AIDS Healthcare Foundation in Los Angeles, commenting on the $1,000 per day price tag. (*Bloomberg News*, 3 March 2014)

"For patients and industry, this is precedent setting…We clearly appreciate that." Jon Beauchamp, business unit leader at Alexion Pharmaceuticals' UK subsidiary, comments on the March 5 decision of the UK's National Institute for Clinical Excellence appraisal committee, which concluded that the company had not provided justification for its price in light of the manufacturing, research and development costs for a rare disease drug. (*BioCentury*, 17 March 2014)