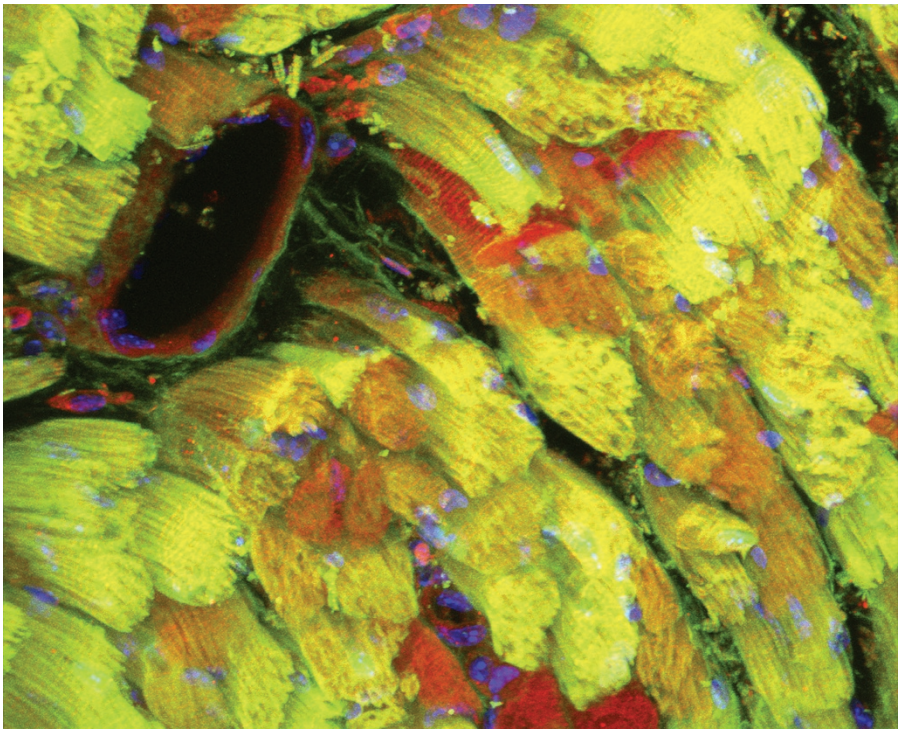
Heart failure gene therapy disappoints but experts keep the faith

The largest study using gene transfer to treat advanced heart failure patients has yielded negative results, its sponsor Celladon announced in April. But experts in the field remain encouraged that the strategy used in the CUPID2 phase 2b trial is sound, and that it will reveal valuable clues for future studies through analyzing dosing and duration as well as the vector and delivery methods. Meanwhile, only days before the San Diego biotech announced its findings, Bristol-Myers Squibb announced an agreement with Amsterdam-based gene therapy pioneer uniQure (*Nat. Biotechnol.* **30**, 807, 2012) for exclusive rights to up to ten gene therapy targets in cardiovascular and other diseases, including its program in congestive heart failure aimed at restoring a calcium sensor, S100A1. Under the collaboration, uniQure receives a $50-million upfront payment and potential milestones and royalties of up to $254 million for the S100A1 program. The New York-based big pharma's buy-in adds momentum to the notion that improvements in the design and delivery of gene therapy may provide the wherewithal to tackle a cardiac indication.

Heart failure is a leading cause of hospitalization in the US and Europe and its incidence continues to grow. This is because although treatments to open coronary arteries after myocardial infarction allow patients to survive longer, they eventually end up with additional myocardial damage. Added to that, an aging population is fuelling heart failure rates.

Celladon began the first human study of gene therapy in heart failure in 2007. The treatment, a genetically targeted enzyme replacement known as AAV1/SERCA2a, is designed to restore impaired calcium cycling—a hallmark of heart failure—and thus help maintain myocardial contractile function. Using the adeno-associated viral vector AAV1, Celladon's treatment delivers the gene encoding the sarcoplasmic reticulum CA^{2+} ATPase (SERCA2a) enzyme, a calcium transporter critical to maintaining calcium homeostasis, which is downregulated in heart failure. Positive results from the initial CUPID phase 1/2 study prompted the company to start enrolling patients in 2012 for the phase 2b CUPID2 clinical trial, which encompassed 250 patients across more than 50 centers in the US and Europe (*J. Card. Fail.* **15**, 171–181, 2009). "A lot of us were very optimistic and hopeful that CUPID2 would meet its endpoint," says Barry Greenberg of the University of California, San Diego (UCSD), who chaired the CUPID2 executive clinical steering committee. "There was a very logical



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Deranged calcium is the hallmark of failing cardiomyocytes. Calcium binding protein is stained red.

Biogen's anti-LINGO promises nerve repair

Biogen's anti-LINGO-1 antibody yielded positive results in a phase 2 trial in acute optic neuritis (AON), a relatively rare disease. The real prize for the company will be if the molecule shows activity in multiple sclerosis (MS). Both conditions result in neuronal damage, and AON can be an early symptom of MS. LINGO-1 (leucine-rich repeat and immunoglobulin domain-containing 1), which is expressed only in neural tissue, prevents remyelination by complexing with the neurotropin $p75^{NTR}$ and NgR1. By using anti-LINGO-1 to inhibit what is stopping myelination, the hope is to instigate remyelination. (Most MS drugs, such as the company's Avonex (interferon beta-1a) and Tysabri (natalizumab), work by inhibiting demyelination.) In the 82-patient, placebo-controlled clinical trial (RENEW), patients receiving six injections of the drug had a 34% improvement at 24 weeks compared to placebo in nerve conduction velocity, that is, the time it took for signals to reach the brain from the retina (the primary endpoint). However, there was no improvement in vision and thickness of the optic nerve (secondary endpoints). Although these results indicate repair had occurred, it remains to be seen how it will work in MS, where patients often enter treatment long after the acute phase, when repair is most likely, is over. Results of the company's phase 2 trial in MS (SYNERGY) are expected next year.

Takeda moves into stem cells

In April, Takeda and Kyoto University's Center for iPS Cell Research Application (CiRA) announced a $270-million, ten-year collaboration for developing clinical applications of induced pluripotent stem (iPS) cells. The work will be conducted at Takeda's Shonan Research Center in Fujisawa, where 100 scientists, 50 from each partner, will be supplied with $170 million in funding over the decade to explore applications in heart, diabetes, neurodegeneration and cancer immunotherapy. Takeda has also committed another $100 million for research services (facilities, equipment and access to Takeda researchers). This deal signals interest from the Japanese pharma sector in stem cells, which has held the attention of the government since Shinya Yamanaka's work on iPS cells won the Nobel prize in 2012. Since then, the Japanese government has been pouring billions of yen into regenerative medicine generally and iPS cells specifically with the establishment of CiRA in 2010, under Yamanaka's direction (*Nat. Biotechnol.* **31**, 272–273, 2013).

> **"It used to be you would call your local news and try to beg them to cover you. Now you build this giant Twitter thing and you make the media come to you."** Arthur Caplan of New York University on Johnson & Johnson's request that he head a panel that will make decisions on compassionate use requests. (*The New York Times,* 7 May 2015)