laureate Paul Nurse, then-president of The Rockefeller University in New York City, became CEO of the joint venture. To help build the structure, the government contributed £220 million; the Wellcome Trust also gave a significant amount.

Construction went relatively smoothly for such a complicated project, observers say. Objections from worried neighbors did not prevent completion of a biosafety level 3 lab for studying diseases such as tuberculosis and influenza. Researchers have their own construction worries, however: The planned route of a new underground railway line was shifted closer to the Crick in 2013. Its vibrations and magnetic interference could affect sensitive devices such as those in MRC's facility for biomolecular liquid-state nuclear magnetic resonance.

The two founding institutes will shift about 900 scientists—including 180 Ph.D. students—and 250 support staff to the new institute by early 2017. As tenured researchers retire, they will be replaced with early career investigators who have a 6-year contract that can be renewed only once. "There will be continual renewal through new people coming in," says Richard Treisman, a scientific director at the Crick. "It's an effective way of keeping a research system lively and vibrant," says Iain Mattaj, director general of the European Molecular Biology Laboratory in Heidelberg, Germany.

Another 200 scientists from University College London, Imperial College London, and King's College London—which each gave £40 million toward construction—will bring in additional expertise during visits lasting from a few months to 6 years. Pharmaceutical giant GlaxoSmithKline will dispatch 20 researchers to work on joint projects with Crick scientists. The proximity to many London hospitals will make translational and clinical research easier.

Some worried that the high cost of living in London might discourage candidates. Mattaj doubts that. "I think the Crick will be a superattractive place." The appeal for Ph.D. students is already clear: Thirteen hundred applied for 44 positions this year.

The United Kingdom's future relationship with the European Union casts a bigger shadow (*Science*, 29 July, p. 437). "It is a blight that is hanging over the whole of British science, but especially the Crick, because it's big and new," says University of London neuroscientist and former MRC chief executive Colin Blakemore. Restrictions on migration could make it more difficult to recruit, Treisman says, and limited access to EU research funds could squeeze the £130 million operating budget, about 5% of which comes from EU grants. "We just don't know what's going to happen." ■

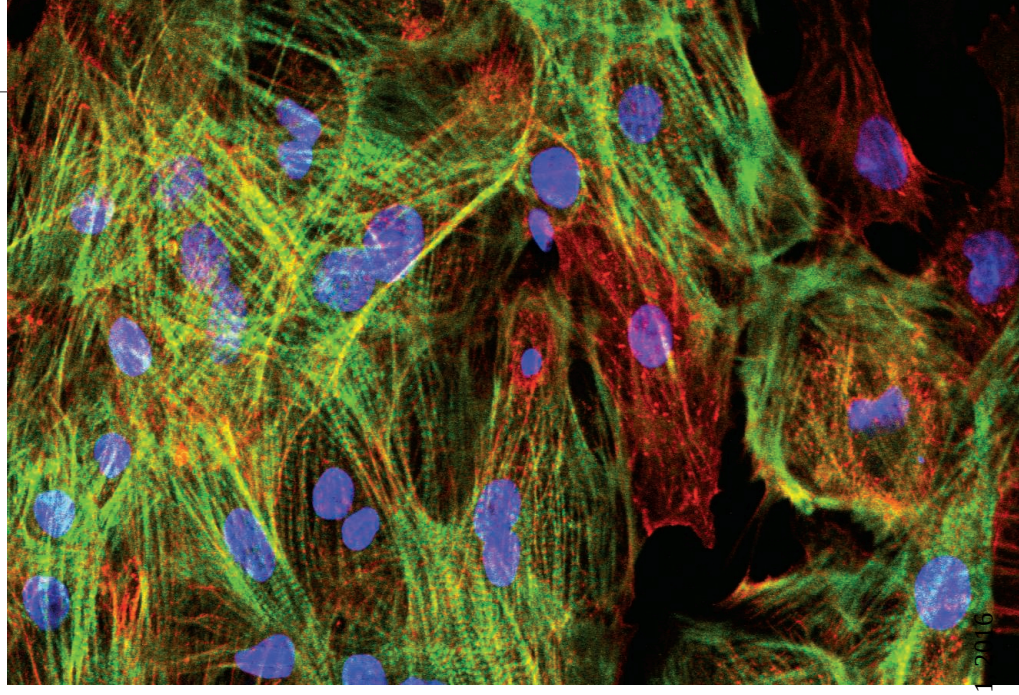

PHOTO: JOSEPH WU LAB/STANFORD CARDIOVASCULAR INSTITUTE

DRUG DEVELOPMENT

A painstaking overhaul for cardiac safety testing

New methods may better predict arrhythmia risk in vitro

By **Kelly Servick**

If any safety test should err on the side of caution, it's one for whether a new medicine might accidentally stop your heart. But for years, researchers have worried that preclinical tests for cardiac risk are so simplistic and conservative that they might lead drugmakers to abandon promising and safe treatments early in development.

Now, an international team of regulators, academic researchers, and drug companies is nearing completion of a project to validate a new—and hopefully more accurate—set of cardiac safety tests, known as the Comprehensive in vitro Proarrhythmia Assay (CiPA). In the coming weeks, a key component of that assay, based on stem cell–derived heart cells, will undergo blind testing on drugs with known risks at various academic and industry labs.

Regulators in the United States, Europe, and Japan rely on standards for arrhythmia risk testing set in 2005 by a body called the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Those standards were born from a series of grim surprises. In the 1990s, several drugs were yanked from the market for dramatic cardiac side effects. One prominent example, an antihistamine called terfenadine, was reported to cause cardiac arrest in more than 100 patients before the U.S. Food and Drug Administration (FDA) withdrew its approval in 1997.

It turned out that terfenadine blocked a key ion channel on the membrane of cardiac muscle cells. Electrical signals from the flow of ions across these membranes rhythmically contract the heart, and this particular channel—encoded by a gene known as *hERG*—helps restore equilibrium after a contraction by letting potassium ions out. If it is blocked, heart cells are slower to "recharge" after a beat, which can lead to an irregular rhythm and sometimes death.

ICH standards require that drug developers test candidates for *hERG*-blocking activity in cultured cells. Not all compounds with *hERG* activity turn out to be dangerous; more than a dozen ion channels interact to affect the rhythm of heart contractions. But researchers spooked by an ominous *hERG* assay sometimes "end up throwing drugs away that most likely would be good drugs," says Gary Gintant, a research fellow at drugmaker AbbVie Inc. in Chicago, Illinois, who leads one of the teams within CiPA. In phase II trials, most drugs get another safety test: Patients' electrocardiograms (ECGs) can reveal potentially dangerous lengthening of the heart's electrical cycle. That process costs millions of dollars, can throw up a red flag after a company is heavily invested in a drug, and sometimes generates both false

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Clusters of stem cell–derived cardiac muscle cells model how the heart may respond to a new drug.

positives and false negatives, Gintant notes.

Better ways to predict how heart muscle will behave would allow drug developers to advance more candidates into trials and maybe avoid large-scale, late-phase ECG studies. Some drug companies and academic labs are already exploring whether channels other than *hERG* are good predictors of arrhythmia risk. They have also begun developing more realistic models of the human heart in a dish, using induced pluripotent stem (IPS) cells—reprogrammed adult cells capable of differentiating into many types of cells. The challenge now is to turn that new science into a well-validated, standard set of tests.

The CiPA initiative, a partnership between FDA and several agencies and consortia, including Health Canada, the European Medicines Agency, and Japan's National Institute of Health Sciences, is an attempt to do just that. One group within CiPA is investigating seven channels (including *hERG*) known to regulate heart rhythm to find which combination of channel-blocking tests might best predict safety. A second team is refining a computer model of the human ventricle's electrical behavior; it will turn ion channel data into estimates of arrhythmia risk. A third is testing how well clusters of IPS-derived heart muscle cells mimic the behavior of the adult heart when exposed to various drugs. Some predict that this stem cell approach, after much refining, could even eliminate the need to test individual ion channels.

In a first round of validation last year, academic and industry labs blindly exposed IPS-derived cells to eight different compounds. Data across study sites "looked surprisingly similar," says Joseph Wu, a cardiologist and stem cell biologist at Stanford University in Palo Alto, California, who led one of the testing efforts.

A second round of FDA-funded tests for a set of 28 compounds began this month. By the end of next year, CiPA collaborators intend to propose the complete assay—a three-part process combining ion-channel assays, computer simulation, and IPS-derived cells—to a group within ICH that could choose to revise the 2005 standard.

Even with this new set of tools, companies may still decide that a compound that acts on multiple cardiac ion channels is too risky to pursue, says Icilio Cavero, a retired cardiovascular pharmacologist and safety consultant to drug companies who is based in Paris. And it will take more than these initial 28 compounds to prove that IPS-derived cells can be reliable safety predictors. "The idea [of CiPA] is beautiful," Cavero says, but "new things scare everybody." ■

DATA: RETRACTION WATCH

RESEARCH MISCONDUCT

Duke fraud case highlights financial risks for universities

Whistleblower alleges doctored data were used to secure $200 million in grants from NIH and other federal agencies

By **Alison McCook**, *Retraction Watch*

On a Friday in March 2013, a researcher working in the lab of a prominent pulmonary scientist at Duke University in Durham, North Carolina, was arrested on charges of embezzlement. The researcher, biologist Erin Potts-Kant, later pled guilty to siphoning more than $25,000 from the Duke University Health System, buying merchandise from Amazon, Walmart, and Target—even faking receipts to legitimize her purchases. A state judge ultimately levied a fine, and sentenced her to probation and community service.

Then Potts-Kant's troubles got worse. Duke officials took a closer look at her work and didn't like what they saw. Fifteen of her papers, mostly dealing with pulmonary biology, have now been retracted, with many notices citing "unreliable" data. Several others have been modified with either partial retractions, expressions of concern, or corrections. And last month, a U.S. district court unsealed a whistleblower lawsuit filed by a former colleague of Potts-Kant. It accuses the researcher, her former supervisor, and the university of including fraudulent data in applications and reports involving more than 60 grants worth some $200 million. If successful, the suit—brought under the federal False Claims Act (FCA)—could force Duke to return to the government up to three times the amount of any ill-gotten funds, and produce a multimillion-dollar payout to the whistleblower.

The Duke case "should scare all [academic] institutions around the country," says attorney Joel Androphy of Berg & Androphy in Houston, Texas, who specializes in false claims litigation. It appears to be one of the largest FCA suits ever to focus on research misconduct in academia, he says, and, if successful, could "open the floodgates" to other whistleblowing cases.

False claims lawsuits, also known as qui tam suits, are a growing part of the U.S. legal landscape. Under an 1863 law, citizen whistleblowers can go to court on behalf of the government to try to recoup federal funds that were fraudulently obtained.

Holding universities liable for research fraud

Whistleblowers have a mixed record of success in False Claims Act (FCA) lawsuits against research universities that involve allegations of scientific misconduct. Highlights from selected cases:

YEAR	WHISTLEBLOWER	DEFENDANT	ALLEGATIONS	OUTCOME
2009	Taryn Resnick, former employee	Weill Medical College of Cornell University	In grants totaling $14 million, researcher Lorraine J. Gudas falsified data, failed to disclose other funding, and misapplied funding.	College settled for $2.6 million, plus attorneys' fees and expenses.
2012	Daniel Feldman, fellowship program participant	Weill Medical College of Cornell University and psychiatrist Wilfred van Gorp	Misuse of research training grant; deviated from submitted plan.	Defendants paid $887,714, plus $602,898.63 in attorneys' fees and expenses.
2012	Kenneth Jones, researcher	Brigham and Women's Hospital, Massachusetts General Hospital, and researchers Marilyn Albert and Ronald Killiany	Including falsified data in application for Alzheimer's disease research grant.	Failed; whistleblower ultimately lost at trial.
2014	Terri King, former associate professor	University of Texas Health Science Center	Falsifying research data.	Failed. U.S. Supreme Court upheld lower court ruling that the public university was exempt from FCA liability.

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Editor's Summary

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