

## BUSINESS

# Biochemist strikes gold

Merck is tapping into academic research in its hunt for drug candidates. Meredith Wadman reports on the company's latest deal with Harvard.

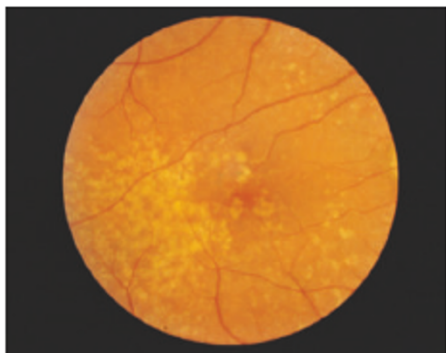
It's the stuff of academics' daydreams: do the science that opens a route to drugs for a common, debilitating and, so far, untreatable condition. Then have a megacorporation swoop in and pay you handsomely for the privilege of — just maybe — turning your labours into a cure.

But in this case, it's no daydream. Late last month, it was announced that Harvard University and one of its biological chemists, Robert Rando, had signed a \$3-million-plus deal with Merck, aimed at developing drugs to battle a leading cause of blindness.

Under the agreement, the New Jersey drug company gets exclusive licenses to a family of candidate small-molecule drugs that Rando, a specialist in the biology of vision, has discovered and patented. The company hopes to find a drug that slows or prevents age-related macular degeneration (AMD) — a disease of the retina that is currently destroying the vision of nearly two million people in the United States alone<sup>1</sup>.

The deal includes undisclosed future milestone and royalty payments from Merck if the company succeeds in developing a drug. "This is perfect," says Rando, "because I absolutely can't do what they are going to do. They are hopefully going to take this basic work and turn it into a drug."

The decision to strike such a deal reflects Merck's determination "to find innovation wherever it's occurring," says Robert Gould, the company's vice president of licensing and external research. In this case, he adds, it was hap-



**Foresight:** Merck strikes a deal that may help find a cure for a retina disease that affects millions.

pening "across the street at Harvard". Gould is based at Merck's two-year-old, 11-storey research laboratory in downtown Boston, right opposite the Harvard Medical School complex (see page 780).

Under Harvard policy, Rando will pocket \$750,000 of the up-front payment — an unusually large amount for a deal between a drug company and an academic investigator. Rando's laboratory, his department and the Harvard Medical School each get the same amount.

Isaac Kohlberg, who heads technology development at Harvard, says the agreement shows a new willingness on the part of pharmaceutical companies to reach further 'upstream' into academic labs in search of promising drugs. "Three or four years ago, if a

project was not in phase II [of human clinical trials], large pharma was not interested," says Kohlberg. "Now, when a project has established proof of principle; the mechanism of action is clear; and you have results in animal studies, they will definitely be interested in acquiring rights."

Merck, Harvard and Rando first started talking last spring. Harvard's technology-development office was already in contact with half a dozen companies about Rando's work. Merck, in the meantime, had come across Rando's papers (see "The science behind the deal"). The company, long involved with ophthalmologic drugs, was drawn to Rando's work on visual-cycle inhibition as an approach to preventing AMD.

"Right from the first conversation, there was a meeting of the minds," says Gould. Soon, Merck's top eye-drug developers, based in West Point, Pennsylvania, made the trip to Boston to meet with Rando and Harvard tech-transfer officials. After several months of pounding out details, the deal was finally signed in February.

The Rando agreement is one of only a handful forged between Merck and academics. These are far outnumbered, so far, by its deals with biotech and drug firms. But the balance may be shifting. "This type of partnership really does represent an important part of our strategy moving forward," says Gould. "It's a harbinger of things to come." ■

1. The Eye Diseases Prevalence Research Group *Arch Ophthalmol* 122, 564-572 (2004).
2. Xue, L., Gollapalli, D. R., Maiti, P., Jahng, W. J. & Rando, R. R. *Cell* 117, 761-771 (2004).
3. Gollapalli, D. R. & Rando, R. R. *Proc Natl Acad Sci USA* 101, 10030-10035 (2004).
4. Maiti, P., Gollapalli, D. & Rando, R. R. *Biochemistry* 44, 14463-14469 (2005).
5. Maiti, P. et al. *Biochemistry* 45, 852-860 (2006).

## THE SCIENCE BEHIND THE DEAL

Robert Rando has spent the last 20 years studying the visual cycle, the complex biochemical pathway by which cells in the retina generate the electrical impulse that gives rise to vision.

Damage those cells — particularly the macula cells in the centre of the retina, which are responsible for high-acuity colour vision — and a characteristic pattern emerges: central blindness. Damage them slowly and chronically, by the build-up of toxic by-products of the visual cycle called lipofuscins, and you

get age-related macular degeneration (AMD). This is a progressive blindness that affects more than one in ten white Americans over the age of 80.

Rando and colleagues first characterized the visual cycle *in vitro* in 1986. After others identified lipofuscins and proposed that they were the toxic culprit leading to cell death in AMD, Rando began a search for visual-cycle inhibitors that he hoped would slow the production of lipofuscins and thus delay or prevent the disease.

To that end, he focused on RPE65, a protein that is essential to the cycle and is found almost exclusively in retinal cells. In two papers in 2004, Rando and colleagues demonstrated that RPE65 is involved in a rate-limiting step in the visual cycle<sup>2,3</sup>. Combine that with the fact that it occurs almost uniquely in the eye, and you have an apt drug target.

By the time the deal with Merck was being fleshed out, Rando already had in hand data for two more papers in *Biochemistry*. The first, published last October<sup>4</sup>,

defined the specific binding patterns of RPE65. In the second, which appeared in December<sup>5</sup>, Rando and colleagues at Columbia University in New York gave small molecule antagonists of RPE65 to mice that had been genetically engineered to produce excess lipofuscins.

The inhibitors, made in Rando's lab, completely blocked the formation of the most common form of lipofuscin found in the eye. That was enough to persuade Merck to pony up that multi-million dollar upfront fee. **M.W.**