

## Roche and Igen in shotgun wedding

On July 24, Roche Holding (Basel, Switzerland) and Igen International (Gaithersburg, MD, USA) ended their seven-year feud over Roche's license to Igen's electrochemiluminescence (ECL) technology, which is used by Roche's diagnostics division. Publicly announced as "Roche to acquire Igen, securing rights to Igen's Origen technology," the deal was more like Hobson's choice for Roche and hitting the jackpot for Igen.

Roche will pay a total of \$1.26 billion, a 27% premium over Igen's closing price of \$37.20 the day before the announcement, and will spin the company back out. Roche will also give the new Igen, which will be 100% owned by Igen shareholders, \$150 million in working capital. In return, Roche receives a nonexclusive license to Igen's technology—to which it once had an exclusive license. In other words, Igen and its shareholders will receive nearly \$1.5 billion and the return of some rights to its own technology.

Both firms are touting this as a 'win-win' situation. But in reality the deal looks much better for Igen: the biotech saw a 60% jump in its share price overnight and will keep Roche as its largest licensee (in fiscal year 2003, Roche accounted for 97% of Igen's royalty income and 63% of Igen's total revenue). In contrast, \$1.5 billion may seem expensive to Roche, considering it was paying Igen only about \$40 million in annual royalties. However, the immunodiagnostic market is estimated to be between \$6–7 billion and Roche is the current leader in this field; its ECL-based lab diagnostics business had sales of over \$400 million in 2002, with a nearly 25% growth rate over the previous three years. Roche apparently anticipates grabbing enough of a market share to make this deal with Igen worthwhile. "Roche obviously did an economic analysis and felt it was worthwhile," says Rick Kaufman, attorney with Heller Ehrman (San Diego, CA, USA).

The story began in 1992, when Igen licensed to Boehringer Mannheim (BMG; Mannheim, Germany) its ECL-based technology (Origen), in which proteins and nucleic acids are coupled to ruthenium chelate and can be detected on the basis of light generated when ruthenium is oxidized/reduced at an electrode surface in the presence of tripropylamine. The license gave BMG the exclusive right to manufacture, market and sell immunodiagnostic products to central hospital laboratories, clinical reference laboratories and blood banks. Igen filed a lawsuit in 1997 against BMG claiming the

firm failed to diligently commercialize the licensed technology and to properly compute and pay royalties owed to Igen, among other things. Roche bought BMG's diagnostics business in 1998, and with it came the Igen license and lawsuit.

"The original license was for 9% royalties, but Roche paid closer to 4–4.5% without renegotiating the contract," says John Putnam, analyst at Belmont Harbor Capital (Chicago, IL, USA).

In January 2002, a jury awarded Igen \$505 million in damages, which Roche promptly appealed. Although the US Court of Appeals for the Fourth Circuit (Richmond, VA, USA) lowered that amount to \$18 million on July 9, 2003, the court's affirmation of Igen's right to

terminate the license agreement with Roche was the key factor in how the situation played out. "Roche can't be in business without it [a license to Igen's ECL technology]," explains Putnam. "Because of the way they [Roche] acted, they basically screwed themselves. Igen essentially had Roche over a barrel."

Both Kaufman and Putnam agree that this is a unique case, but it underscores the benefits to small biotech companies of sound intellectual property management. Although Igen's original ECL patent was granted in 1991, and will expire in 2011, the firm has regularly patented improvements on the technology (most recently in 1999) to expand the life of its patent portfolio.

Aaron Bouchie, New York

## Resistance to *Bt* toxin surprisingly absent from pests

Defying the expectations of scientists monitoring transgenic crops such as corn and cotton that produce insecticidal proteins derived from *Bacillus thuringiensis* (*Bt*), target insect pests have developed little or no resistance to *Bt* crops thus far, according to US Department of Agriculture-funded scientists. These findings suggest that transgenic *Bt* crops could enjoy more extended, more profitable commercial life cycles and that the measures established to mitigate resistance before the crops were introduced are paying off.

"If I'd gotten up seven years ago and said that there would be no evidence of increased *Bt* resistance after *Bt* crops were planted on 62 million hectares [cumulative and worldwide], I would have been hooted off the stage," says entomologist Bruce Tabashnik of the University of Arizona (Tucson, AZ, USA), whose research group recently completed a survey of this phenomenon in collaboration with scientists from Cornell University (Geneva, NY, USA). "No one predicted that there wouldn't even be a minor increase, which is extraordinary."

Nor has Monsanto (St. Louis, MO, USA) seen any signs of resistance to transgenic *Bt* crops, despite widespread use in a number of countries. Graham Head, who is responsible for global coordination of insect resistance management at Monsanto, agrees with Tabashnik's explanation of these findings: "the use of refuges to manage resistance that



The diamondback moth is the only pest to have evolved resistance to *Bt* sprays used by organic growers, but no pest has evolved resistance to transgenic *Bt* crops in the field.

tends to be recessive and have fitness costs is a highly effective means of delaying resistance," says Head.

*Bt* transgenic corn entered the commercial arena in 1996 amid extensive, sometimes contentious deliberations over steps needed to avoid or at least retard what some scientists considered the inevitable development by target insects of resistance to these insecticidal proteins, which are encoded in genes carried by soil-dwelling bacteria. Officials at the Environmental Protection Agency (EPA; Washington, DC, USA), working closely with researchers from universities and industry, specified measures for this purpose.

The primary resistance-preventive measure

that farmers who plant transgenic *Bt* crops are required to take is to set aside some acreage (see p. 1003) as refuges on which they grow varieties of the same crop devoid of *Bt*. Carefully developed population genetics models indicated that such *Bt*-free refuges would permit susceptible insects to survive and swamp out resistant variants that might emerge from the pest population feeding on *Bt* plants in nearby fields.

Although *Bt* plantings were modest at first, farmers in several countries enthusiastically adopted this technology and now plant about 10–15 million hectares of *Bt* corn and cotton annually, mainly in the United States, Argentina, Australia and China. *Bt* potatoes were once grown commercially on a smaller scale, while *Bt* canola and broccoli are being grown in labs and greenhouses to evaluate *Bt*-resistant insect pests.

*Bt* resistance is not merely a theoretical concept, according to Tabashnik and other researchers. For example, *Bt*-resistant mutants of the European corn borer are readily identified in the lab, says Tabashnik. Similarly, Kongming Wu at the Chinese Academy of Agriculture Sciences (Beijing, China) and his collaborators find that isolates of *Helicoverpa armigera*, a bollworm that feeds on several crops, including cotton, corn, and peanuts, in the Yellow River Valley in China developed measurable resistance to *Bt* following multiple generations of exposure to *Bt* toxin in the laboratory. Nonetheless, based on field monitoring during the past five growing seasons (through 2002), Wu found no discernible increase in the resistance of this bollworm to *Bt*-cotton being grown commercially, and the frequency of resistance alleles in field populations is still low.

The absence of *Bt* resistance “does not seem surprising to me,” says Gary Fitt, who is Strategy Director of CSIRO Entomology (Narrabri, Australia). Australians began growing *Bt* cotton in 1996, beginning with about 10% of the total cotton crop of about 500,000 hectares and now plant at an agreed-upon cap of 30%, or about 180,000 hectares. “The cap was an additional level of conservatism above our resistance management strategy,” he says. “The strategy includes refuges, [a] planting window, mandatory crop residue destruction, management of volunteer plants and thresholds for pest management.”

This same pattern of little or no *Bt* resistance holds true for *Bt* corn and *Bt* cotton grown elsewhere, including the United States, despite occasional unverified reports to the contrary, Tabashnik says. “More than 500 species of insect have evolved resistance to

one or more conventional insecticides. So far, the track record for *Bt* is better. In the field, only one pest, the diamondback moth, has evolved resistance to *Bt* sprays, and none has evolved resistance to *Bt* crops. Despite this success, the incredible adaptive ability of insects means that resistance remains a threat.”

“The main question is whether we don’t see

resistance because the EPA has instituted the high-dose, refuge approach or whether we never needed a resistance management approach in the first place,” says Fred Gould of North Carolina State University (Raleigh, NC, USA), who also is studying *Bt* resistance in the US and with Wu in China. “This is a tough question to answer.”

Jeffrey L Fox, Washington

## Roche’s microarray tests US FDA’s diagnostic policy

In what could prove to be a landmark test case for the burgeoning field of microarray diagnostics, the US Food and Drug Administration’s (FDA; Rockville, MD, USA) division of *in vitro* diagnostics sent a letter to Roche Diagnostics (Basel, Switzerland) regarding the marketing of its AmpliChip CYP450 Array. The FDA does not regulate any microarrays that are currently on the market, and how the agency classifies the AmpliChip could have implications for similar diagnostic tool kits in the pipelines of at least ten other companies.

Roche launched AmpliChip in late June 2003 for use in clinical diagnostic laboratories to determine a patient’s genotype with respect to two genes that govern drug metabolism. The information could be used by physicians to select the best drug and dosage for a given patient for indications including cardiovascular disease, high blood pressure, depression and others, according to Roche.

The FDA’s problem with AmpliChip is that Roche began marketing the product as an analyte-specific reagent (ASR) and a class 1 medical device, which don’t need premarket applications (PMA). A PMA requires clinical demonstration of safety and effectiveness that can take three years and can cost around \$750,000, says Ralph Martel, vice president of multiplexed technologies for High Throughput Genomics (Tucson, AZ, USA).

The FDA believes that the AmpliChip cannot be classified as an ASR, because it is not limited to detection of a single analyte, nor is it a set of reagents for laboratories to use to create their own diagnostic tests. Rather, it is a complicated device with specific directions that, if misused, has the potential to harm patients through misdiagnoses. The FDA says the AmpliChip may be better classified as a class 2 or class 3 medical device, which would likely require



Roche’s AmpliChip is proving to be a test case in the use of microarrays for human diagnostics.

a PMA, says Areta Kupchyk, counsel for law firm Reed Smith (Washington, DC, USA) and former associate chief counsel for the FDA’s Center for Biologics Evaluation and Research.

The FDA’s letter, dated July 8, does not threaten Roche, but asks the company to work with the agency to find a new classification for AmpliChip. Indeed, Roche may have anticipated the FDA’s actions. According to a report in *BioArray News* (3, 32, 1–6, August 6, 2003), Roche teamed with Becton Dickinson (Franklin Lakes, NJ, USA) and Gen-Probe (San Diego, CA, USA) to send a letter dated June 17 to the FDA calling for a new category of diagnostic called *In Vitro* Analytical Tests (IVAT), which, if adopted, would not require PMAs. The document does not mention the AmpliChip specifically, but it does describe