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Partnering/Licensing

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Getting dumped

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Many biotech products experience setbacks and disappointments along the path to commercial success. Here, three industry insiders provide some suggestions for the best practice when a product is returned or discontinued by a licensee.

Mike Clark was at work in the University of Cambridge's Department of Pathology in the UK when he got an e-mail from a colleague: Glaxo-Wellcome (London, UK) had returned rights to the humanized monoclonal antibody Campath (alemtuzumab) that Clark had championed, which was in phase 3 trials. Had he not already been in a chair, Clark would have had to sit down to digest the news—the product that he had spent the better part of his professional life working on now had no port to call home.

"It was a big blow," he says. "I must admit that for a while it was incredibly disappointing. If you think back, I'd been working on that antibody project since 1981, so that represented 15 years of hard work and data, and it was all going down the plughole very rapidly."

That is often the nature of drug development: deals are broken, products are returned and collaborations fall apart. In the following article, three industry insiders—from a biotech firm, tech transfer and academia—provide their viewpoints on the best strategy to rescue a project on the brink of commercial extinction.

Jilted by a pharma partner

The predominant view is that there has never been a better time for biotech firms to obtain licensing agreements and to cut partnering deals on favorable terms with large pharma. But what happens when those deals go bad? The biotech sector is replete with examples of big pharma companies returning product to a small biotech, often on the basis of commercial reasons (Table 1). What's more, a smaller firm's lifeline may be attached to the agreement, and losing the partner can be a devastating blow that requires regrouping and a change in direction.

Take Waltham, Massachusetts–based Oxigene. In 2001, it was anxiously watching the commercial prospects of its lead product—combretastatin A4P (CA4P), a cytostatic compound derived from the African tree *Combretum caffrum*—shrivel in the hands of partner Bristol-Myers Squibb (BMS; New York). BMS just so happened to be in the process of preparing to in-license the cancer drug Erbitux (cetuximab) from New York–based ImClone Systems. Throw in some phase 1 adverse events with CA4P, which is designed to inhibit microtubule assembly in dividing cells, and BMS no longer seemed interested.

"It was clear that Bristol-Myers had reprioritized their portfolio," says Richard Chin, Oxigene's CEO and president. "The effort they were putting into the drug was starting to be less than what we thought was appropriate. It's not great to have a partner if they are not moving the

drug along as quickly as you might want. In fact, it's better to get the drug back, rather than have it languish."

Oxigene's management took the initiative; company executives approached BMS and opened up a dialog, explaining that if BMS was not going to move the product forward, Oxigene wanted rights back. BMS agreed to turn over rights, but wanted to keep the backup compounds. Oxigene's team responded: No, they said, we need the backups too.

When the negotiating was done, Oxigene officially licensed CA4P back from BMS, with a royalty stream attached, contingent on approval. It was a satisfactory ending for Oxigene: the deal was initially struck in late 1999 and was valued at up to $70 million for the biotech. Even with the early termination, it received $10 million up front, and BMS spent "in the tens of millions" developing CA4P, having conducted three phase 1 trials, Chin says.

With the compound back in house, Oxigene next had to decide how to move forward. It had only ~$20 million in cash—not enough to continue clinical development solo—but was a public company and could tap the markets for more. It decided not to immediately repartner, and instead it discontinued development of another drug in its portfolio, the benzamide-based declopramide, to help cut costs. Today, the company is again seeking a partner to help with commercialization and has CA4P (now called Zybrestat) in multiple clinical trials for various oncology and ophthalmic indications, and it is looking to start a phase 3 trial in anaplastic thyroid cancer. Oxigene also has OXi4503 in phase 1 cancer studies and several research programs. CA4P is the only product that Oxigene has had returned, but there are lessons to be learned here.

When shaping a deal, especially if there is a bidding war for the product, as there was for CA4P, "you have to consider not just what happens if all goes well, but what happens if [the product] gets deprioritized in the eyes of the partner, or if you run into setbacks, or the partner isn't very committed," Chin says. And once the deal is signed, make sure you have a champion for that product somewhere inside the partner company, a person who will stand up for it when it hits snags.

Structure the license to include development milestones, such as filing an investigational new drug application by a certain date. If those milestones are not hit, it might give the licensor the right to ask for the product back.

Chin has more advice: when it becomes clear that the product is hung up or is no longer top priority with the licensee, go get it. It won't be pleasant—if your company is public, the stock will take a short-term hit, and observers might view the drug as tainted, meaning it will be harder to repartner later. But an idea gathering dust on a shelf someplace isn't the answer, either.

One final caveat: before asking for any product back, make sure there is enough money to advance it in house, because it is nearly impossible to line up a new partner when it is still tied to someone else. For Oxigene, the public markets were there to help, but for private firms, that means approaching your backers with the begging bowl.

Most importantly, though, is to "never forget that the drug is your drug," Chin says, which means if you're not happy with the partner's pace of development, do something about it.

Industry-university breakups

As many discoveries are spun out of academia, technology transfer offices also have their fair share of setbacks in licensing. The Massachusetts Institute of Technology (MIT; Cambridge, MA) completes about 120 licenses a year—about 35% or 40% of which are biotech products. Of those licenses, about 100 go to existing companies and the remaining 20 to spinouts or startups. MIT estimates that only 5–10% of out-licensed products or technologies are returned, but when they are, it is often more about money than anything else.

Andrea Schievella, a technology licensing officer at MIT, explains: "That's what just happened to us recently," she says. "The technology [a mouse model] didn't work as everyone had hoped, and because of that, the company could not raise enough funding to keep going."

The firm had looked around for a buyer and talked with a potential acquirer before negotiations fell apart, all of which MIT was aware of—Schievella says that "if you are doing a good job" as a licensing officer, there should be no surprises.

MIT's licensing contracts stipulate that the licensee can terminate a contract for any reason, so long as it provides six months' notice. MIT, on the other hand, can terminate a deal if contractual milestones are not being hit, if the company is failing diligence requirements or if it is not able to pay its bills. In this case, scenario three came into play.

Because MIT was not convinced the cash-strapped firm was able to support the development of its product, the technology transfer office looked around for another industrial partner (and found interest from the firm that had failed to acquire the company holding the license). With a partner in mind capable of reviving the stalled project, MIT went to the financially unstable firm and "terminated the license," Schievella says. Today, the second company has a one-year option on the technology, at which point it will decide whether to officially license it.

From this and other experiences, Schievella believes there are several simple steps that should immediately be taken when a product is returned

from a company (see Box 1).

An interesting wrinkle to academic licensing is the issue of patents. Whether the invention or product is patented will determine how eager universities are to license it out—or how quickly they think they should relicense it following a broken deal.

For issued patents with paid-up maintenance fees, MIT actively pursues the relicensing of returned technologies. But if that four-year window between maintenance fees runs out without a suitable licensee being found, the university might shelve the product rather than pay another fee.

If a returned product is engaged in any ongoing patent litigation, MIT waits until the matter is settled before deciding what comes next. With a patent undergoing the application process, which is more expensive than maintenance, decisions to drop or seek a new licensee are made quicker. In general, though, Schievella says, "We always want to get our technology licensed."

Return to sender

So, whatever happened to Mike Clark and his collaborators—Herman Waldmann, Geoffrey Hale, Stephen Cobbold, Lutz Riechmann, Gregory Winter, Jenny Phillips, Martin Dyer, Robert Marcus, Martin Lockwood, Peter Mathieson and David Oliveira—who discovered and developed Campath?

The history behind the product testifies to how checkered and tortuous the passage of a product to commercial success can be.

Campath was originally licensed to Burroughs Wellcome (Research Triangle Park, NC) through London's BTG (known as British Technology Group before its 1995 flotation), which was originally launched by the UK government to protect the intellectual property (IP) rights of British inventions developed with public funds. Clark and his group gave BTG control in return for milestone payments and royalties, and BTG subsequently licensed the antibody to Burroughs Wellcome, which took the antibody through clinical trials for lymphocytic leukemia, lymphoma and rheumatoid arthritis. By the time Campath was in late-stage trials, Burroughs Wellcome was in the process of merging with Glaxo Pharmaceuticals (London) and decided to discontinue Campath's development.

Once the rights to the drug were back in the hands of BTG, Clark and his collaborators were able to influence the next step. Through personal contacts at LeukoSite, they put BTG in touch with the Cambridge, Massachusetts–based startup, which in-licensed the product from BTG in 1997. The inventors also had the option to obtain the rights for Campath back from BTG if the latter had not been able to relicense it.

This was not the end of the story, however. LeukoSite was in turn acquired by Millennium Pharmaceuticals (Cambridge, MA), which then formed a 50/50 partnership with ILEX Oncology to develop Campath. The drug gained accelerated approval from the US Food and Drug Administration (Rockville, MD) in December 2000.

Millennium later divested its interest in Campath to ILEX, which meant that when Genzyme (Cambridge, MA) bought ILEX in 2004 for ~$1 billion, Genzyme acquired full rights to Campath. Genzyme is still developing the drug in other indications, but it is approved for relapsed B-cell chronic lymphocytic leukemia and has brought in hundreds of millions of dollars since it was launched in the United States and in Europe (where it is called Mabcampath) in 2001.

That was a different time for drug development, with technology transfer offices still in their infancy, and Clark admits that today inventors would not have the same influence that he and his group had in the nineties. Even so, he believes the events are instructive to other inventors who have an interest in seeing that their products are not shelved by a technology transfer office if they are returned from a company (see Box 2).

What led Glaxo-Wellcome to return Campath anyway? Clark says that "it's hard to know exactly why" the pharma firm let it go, but he thinks it has to do with the market potential. The product was being used off-label for bone marrow transplantations at the time, but although the lymphoma data were looking good, he thinks Glaxo-Wellcome might have wanted to branch into rheumatoid arthritis. When early data weren't glowing, it backed out.

Another factor is that this was 1995, and antibodies had not yet validated themselves as drugs. Clark points out that had Campath continued uninterrupted down the development path, it would have become the first recombinant antibody on the market, and there was no guarantee that the public or doctors would have adopted it.

"[Glaxo-Wellcome] had estimated the market size for antibodies would be quite small," Clark says. "Retrospectively, that turns out to be completely wrong."

Table 1: Select terminated industry collaborations from 2006

Company	Partner	Product	Product status today
Antisoma plc (London)	F. Hoffmann- La Roche Ltd. (Basel, Switzerland)	Antisoma regained all rights to the investigational cancer drug AS1404 from Roche, saying that it planned to move the agent into phase 3 trials in lung cancer. (June 2006.)	Antisoma attracted Novartis as new development partner in April 2007. Deal calls for $75 million upfront to Antisoma and $25 million upon Novartis starting phase 3 trial in lung cancer. Total milestones could reach $890 million. Novartis plans to begin phase 3 in lung cancer and prostate cancer in 2008. Drug renamed ASA404.
Nastech Pharmaceutical Co. Inc. (Bothell, Washington)	Merck & Co. Inc. (Whitehouse Station, New Jersey)	Merck ended its deal to develop the PYY3-36 nasal spray for obesity. Merck made the move after review of data from a proof-of-concept study; Nastech intends to continue the program, with a dosing study followed by a phase 2 trial. (March 2006.)	Nastech plans to conduct a phase 2 trial in the second half of 2007. Trial is expected to have around 500 patients, and its results will drive next steps.
PDL BioPharma Inc. (Fremont, California)	Hoffman-La Roche Inc. (Nutley, New Jersey)	Roche ended its involvement in the development of daclizumab for asthma, a deal begun in 2004. (August 2006.) Roche also ended a deal to develop daclizumab in organ transplantation, originally started in 1989. PDL holds all rights in both indications. (November 2006.)	PDL is searching for new partner. Will commence phase 2 studies in both indications once partner is secured.
Curis Inc. (Cambridge, Massachusetts)	Genentech (South San Francisco, California)	Curis opted out of 2003 deal to codevelop a topically administered Hedgehog antagonist basal cell carcinoma drug. The companies had previously stopped enrollment in a phase 1 trial; other collaborations between them were not affected. (September 2006.)	Genentech decided not to move forward with the topical formulation, but the companies continue work with a systemic Hedgehog antagonist formulation.

Source: BioWorld

Box 1: Starting over

Wondering how to resurrect a promising product if it has been returned to the technology transfer office from which it was originally licensed? Andrea Schievella, a Technology Transfer Officer at MIT, suggests some places to start the process.

Step 1. Contact original inventor to see if he or she knows of companies that might be interested in the product.

Step 2. Go directly to other companies working in the same area and gauge their interest.

Step 3. If the product is under patent application, contact a patent attorney to see how likely it is that the patent will be issued. If the patent is issued, explore how commercially useful the claims are likely to be, thus helping to decide whether it is worth pursuing another partner.

Step 4. Contact the company that is returning rights and see whether management knows of anyone interested in licensing the product. Often, they will have had a company contact them for a sublicense, but not have acted on the request for competitive reasons.

Box 2: Words of wisdom

Mike Clark encountered more than his fair share of highs and lows in the development of Campath. Some of his thoughts on how to optimize the product licensing process and commercial development are provided below.

Prepare before licensing. When constructing a license, stipulate that if the licensee changes direction and does not plan to develop the product, rights revert. Alternatively, include clauses covering expected development milestones and pace of development. “I think those clauses are quite good to have in,” says Clark. “You don't want your licensee to be able to sit on your idea and not do anything to it.”

Rally the troops; take all you can. After hearing about a product return, get together everyone involved and discuss what can be salvaged, and how. For Clark and Campath that meant dealing with the antibody's patent, which still had not been issued in the United States. Other team members worked with BTG to get back the original data, but also the new data generated since the license was enacted, which took some persuasion. Another issue here is contract specificity: insist on clauses that return not only the original IP, but also any ancillary IP that might be required for further development. “That's certainly something to push for,” Clark says. “If a company is going to abandon it, it seems a shame not to have the product pursued, since it might give benefit to patients.”

Finding someone new. Once the product and everything attached is back in house, it's time to find a new partner. The key, Clark says, is to locate a company that strikes a balance—it needs the “tens of millions of dollars” required to do the trials, but should not have “so many balls in the air that your product gets lost.” Looking back, he feels it might have been better to work with a smaller company than Glaxo-Wellcome right from the start. Once a new partner is in place, get in tight with the senior scientists.

Don't give up. The reason Campath is on the market today is “persistence and dogged determination, and optimism and belief in our own ideas,” Clark says. “There were many times when it would have been easy to abandon the project, but if you have a firm belief in your own ideas, then you are the only one who can put the pressure on and keep pushing.”