an infection, particularly useful in people with compromised immune systems. The beauty of this peptide is that its mechanism of immunomodulation appears to be entirely different from that of previously described peptides, which can induce inflammation, counteracting any potential benefit. This finding, too, has led to patent applications, one of which has been licensed exclusively to Inimex, whereas others are being developed through the Grand Challenges program. Hancock has great hopes for these peptides; the Inimex-licensed peptides are almost ready to go into the clinic.

According to Barbara Campbell, who, as associate director of the University Industry Liaison Office at UBC, has been handling Hancock's portfolio for the past seven years, establishing commercialization strategies has been a collaboration between her office and Hancock. Once an inventor gets involved with a company, the tech transfer office gets interested, but once multiple companies are involved, then they really have to step up and make sure that there are no areas of overlap that can be costly in time and legal fees. Although working with Hancock has created a lot of work for her, he makes her job easier, as his extensive experience makes him sensitive to these potential pitfalls.

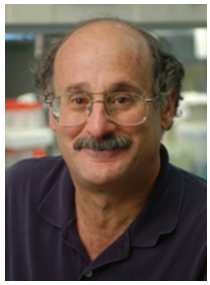
Despite all this commercial activity, Hancock describes himself as a basic researcher. He says he's learned from experience that without a basic understanding of mechanism, a potential drug will never make it through development. And when Bob Hancock speaks, people listen—he has sat on no fewer than 17 scientific advisory boards, a clear sign that his expertise is appreciated by his peers.

1. Hilpert, K. *et al.* High-throughput generation of small antibacterial peptides with improved activity. *Nat. Biotechnol.* **23**, 1008–1012 (2005). (This paper has been cited 27 times according to Thomson ISI Web of Knowledge. In the references following, the number of citations appearing in parentheses at the end are all based on Thomson, October 12, 2007.)
2. Scott, M.G. *et al.* An anti-infective peptide that selectively modulates the innate immunity response. *Nat. Biotechnol.* **25**, 465–472 (2007). (3 citations)

Out of left field, into the mainstream

Group II introns are not the stuff of headlines, but for the past 15 years, University of Texas's (UT; Austin) Alan Lambowitz has been working away at these tiny mobile elements. His work has spawned an actual product—TargeTron, a gene disruption kit sold by Sigma Aldrich—numerous patents, a company and a raft of publications showing how introns can be used to engineer otherwise recalcitrant, yet clinically important species like the human pathogens *Staphylococcus aureas*[1] and *Clostridium difficile*[2].

Having found that group II introns—which are self-catalytic mobile genetic elements—integrated into DNA through base pairing, Lambowitz demonstrated in his 2001 *Nature Biotechnology* publication[3] how they can be used as gene targeting agents. He and his coworkers demonstrated retargeting of the *Lactococcus lactis* Ll.LtrB intron to bacteria other than its natural host species by modifying its integration sequence. In addition, they showed that the intron, in combination with an associated intron-encoded DNA endonuclease, introduces double-stranded breaks in the DNA, creating a template for homologous recombination, similar to the mechanism of zinc-finger endonucleases.



Alan Lambowitz is gearing up to expand his gene targeting technology into new areas.

Since then, Lambowitz's group has improved the efficiency of integration tenfold, using a computer algorithm to optimize integration, which purchasers of TargeTron can use to design their own introns. And they (and others) have racked up an impressive number of species as well as genes that have been targeted with this system—some 45 genes and 16 different bacterial species are listed on the TargeTron pages on the Sigma Aldrich (St. Louis) website (http://www.sigmaaldrich.com/Area_of_Interest/Life_Science/Functional_Genomics_and_RNAi/TargeTron.html).

Lambowitz acknowledges that the system hasn't reached its stride yet. "It comes from out of left field," he says. But he still thinks that its time will come—after all, although the technology is now six years old, the kit has been available only for two years, work on expanding the host range has come out just this year, and more importantly, he feels its advantages have yet to be fully appreciated. The most important among them, according to Lambowitz, is that group II introns can be used in species without well-developed genetic systems, as demonstrated independently by the work of Nigel Minton, at the University of Nottingham, UK[2]. Minton has developed a set of introns that he has used to target several *Clostridium* species, starting with the TargeTron kit (he calls his introns "the Clostron"[2]), and testifies on his website to the importance of the gene disruption technology. "Twenty-one genes in a few short months equivalent to [the] last 20 years [of] published achievements" he writes. (http://hcai.nottingham.ac.uk/minton.pdf)

Lambowitz's laboratory has recently scored a major breakthrough for the technology by showing that group II introns can target mammalian genes. And given their ability to generate double-stranded breaks, this provides a potential alternative to zinc-finger nucleases for initiating homologous recombination and gene replacement, with a technology that might be more accessible than zinc fingers. "[People] don't need trade secret zinc-finger libraries. Anyone who goes to Sigma Aldrich or our website can design an intron that can insert," says Lambowitz.

The path to commercialization started at Ohio State University (Columbus), where some of the early work was done, resulting in the creation of a licensing entity, Ingex (St. Louis), which is still in business today and holds technology described in the *Nature Biotechnology* paper in its intellectual-property portfolio. Moving to the University of Texas in Austin, where Lambowitz now heads the university's Institute for Cellular and Molecular Biology, did create some interesting challenges, but Lambowitz declines to elaborate because the three entities (the two universities and Ingex) have since worked out an arrangement that suits them all.

And UT is now looking at a second generation of startups, based on the expanding Ingex portfolio, which, according to Greg Pogue, UT's technology transfer manager for the Lambowitz work, will take the technology to the next level and into applications as diverse as cancer and biofuels. According to Pogue, the technology has stepped over a significant barrier, in demonstrating that it can be applied to both bacterial and eukaryotic genome engineering. This opens up a host of possibilities and Pogue, himself a former biotech researcher and executive with 35 publications and 12 patents to his name, is using his contacts in the industry to identify appropriate partners for developing particular applications.

1. Yao, J. *et al.* Use of targetrons to disrupt essential and nonessential genes in *Staphylococcus aureus* reveals temperature sensitivity of Ll.LtrB group II intron splicing. *RNA* **12**, 1271–1281 (2007).
2. Heap, J.T. *et al.* The ClosTron: A universal gene knockout system for the genus *Clostridium*. *J. Microbiol. Methods* **70**, 452–464 (2007).
3. Karberg, M. *et al.* Group II introns as controllable gene targeting vectors for genetic manipulation of bacteria. *Nat. Biotechnol.* **19**, 1162–1167 (2001). (31 citations)