

Innovations

Bug warfare IntraBiotics Pharmaceuticals, Inc.

Chemistry & Biology November 1999,
6:309–310

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Twenty companies in the San Francisco Bay Area each hauled in US\$20 million or more of venture capital in the first quarter of 1999. Nineteen of those companies aim to make money from the internet. The lone biotech, almost lost in the sea of dot coms, was IntraBiotics Pharmaceuticals, Inc. (Mountain View, California).

Former venture capitalist Kenneth Kelley started IntraBiotics in 1994 with the idea of using a big pharma strategy — technology piracy — against the mounting problem of antibiotic resistance. “I realized,” says Kelley, “that I could form a company, and skip the three or four years of pre-clinical discovery time.”

Success, complacency and panic

Penicillin, the first antibiotic, was discovered by Alexander Fleming in 1928, and first used to treat humans by Howard Florey in 1941. It was a miraculous development for soldiers injured in World War II. Within a few years, however, physicians detected penicillin-resistant bacteria. Methicillin was used as a replacement, but by 1992 ~40% of hospital strains of the common bacterium *Staphylococcus aureus* were the methicillin-resistant, or MRSA, form.

The last line of defense was the glycopeptide vancomycin. In 1987, vancomycin-resistant *Enterococcus faecalis* (VREF) appeared in England and France, quickly spreading to the United States. VREF threatens only those with compromised immune systems, but in 1997 partial resistance

to vancomycin was detected in patient isolates of the more virulent *S. aureus* both in Japan and the United States. Fully vancomycin-resistant *S. aureus* (VRSA) is something that Richard Locksley, an infectious diseases expert at the University of California, San Francisco, and member of the IntraBiotics scientific advisory board, calls “a particularly terrifying prospect.”

Big pharma was caught napping. “There was a big lull [in antibiotics research] in the 70s and 80s, following on the heels of some really superb drugs like the third-generation cephalosporins, and some high ranking comments that infectious diseases were dead,” says Locksley. “The rise of HIV put an end to that.”

Search for inspiration

In 1993 Kelley went searching for his founding technology. “The antibiotics crisis had by then moved from the technical literature to the lay press,” says Kelley. So when Kelley toured several laboratories at the University of California, Los Angeles, naturally Robert Lehrer’s was amongst them. Kelley knew of Lehrer’s work on defensins — peptides made in neutrophils that help destroy ingested bacteria.

A small company takes the big pharma approach — judicious poaching of others’ technology.

But Lehrer wanted to talk about protegrins. “[Kelley’s] timing was impeccable,” says Lehrer. “He came to talk to me about defensins, but I said, ‘We have something that is actually better.’”

The protegrin story started with Russian researcher Vladimir Kokryakov, who Lehrer met when he was visiting his son in St Petersburg. Kokryakov moved his cash-starved research to UCLA, and with Lehrer found several antimicrobial peptides in pigs that, compared to defensins, were half the size, more potent, and resistant to salt inhibition.

IntraBiotics is starting a phase III trial for oral mucositis with a modified, 17-amino-acid version of protegrin-1 (Figure 1). Chemotherapy patients are given a mouthwash to kill the wide range of bacteria that invade tissues damaged by anticancer drugs. Most antibiotics fail to kill all the different types of colonizing bugs, but protegrin is active against both gram-positive and gram-negative bacteria.

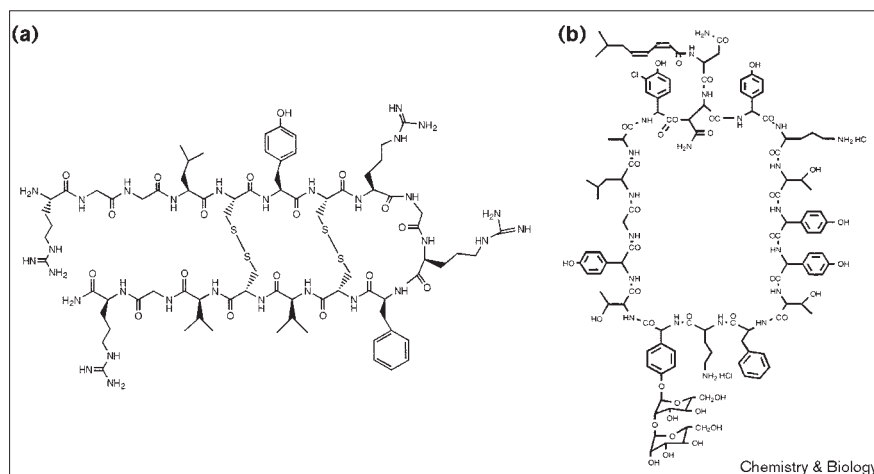
Protegrins as a test case

Protegrins are representative of a newly discovered but ancient class of antibiotics — the antimicrobial peptides. Whether derived from silkworms, crabs or cows, they work by either forming pores or otherwise disrupting membrane structure. Their selectivity for bacteria arises largely from their cationic charge: bacterial cell membranes have greater negative charge, and a higher electropotential gradient. The absence of cholesterol and presence of lipopolysaccharide may also be important.

Resistance to protegrins has not been seen *in vitro*, perhaps because of this mechanism of action. “To fundamentally alter the characteristics of the cell membrane requires a lot of changes at once,” says John Fiddes, IntraBiotics’ vice president for research and development.

IntraBiotics is trying an aerosol of protegrin-1 for lung infections, but Fiddes says “there’s no really good expectation for systemic protegrin use” because the cationic peptides are so sticky and do not penetrate tissues. These physical characteristics may explain why other companies interested in antimicrobial peptides are also trying topical indications.

An alternative explanation comes from Robert Hancock (University of British Columbia, and an adviser at Micrologix Biotech Inc., Vancouver, Canada; see Table 1). He says that trials for topical indications are simply cheaper and easier. As for the problem of stickiness, he says, “there’s always the possibility of judicious formulation to get around that. A liposomal formulation might work.”



Similar structures but contrasting mechanisms of action. The protegrin-1 analog IB-367 (a) forms a tight anti-parallel β -sheet

that disrupts membranes, whereas ramoplanin (b) inhibits an enzyme involved in cell wall synthesis. Figure courtesy of IntraBiotics.

The first antimicrobial peptide trials were run by Magainin Pharmaceuticals Inc. (Plymouth Meeting, Pennsylvania) using the magainin peptide from frog skin. Initial trials against impetigo (a skin infection usually seen in children) showed no difference compared with controls. (“If the kids scrubbed their faces with soap and water they got better,” says Kelley.) Then a second phase III trial for infected foot ulcers in diabetic patients was conducted using a comparison with an existing antibiotic. The FDA wanted a placebo trial and refused to approve the drug.

Kelley says his medical indication and drug are quite different. But Magainin’s rejection, and the departure of another company into

selling health bars on the home-shopping network (Table 1), has had an impact. “With the two failures of Magainin, the feeling is that no one company will succeed, so it has to be cooperative,” says Hancock. “I think Micrologix is hoping that IntraBiotics will succeed, and vice versa. One success will be considered a flash in the pan, but two successes might be considered a movement.”

The next candidate

With protegrin safely in trials, Kelley asked his dedicated team of literature searchers to find an abandoned but promising lead. The result was ramoplanin, a cyclic peptide isolated in 1984 from an *Actinoplanes* culture by what is now termed Biosearch Italia,

S.p.A. (Gerenzano, Italy). After being spun out from Hoechst Marion Roussel, Biosearch did not have the resources for clinical development. Kelley pounced on ramoplanin as a potent antibiotic with no sign of resistance development *in vitro* and a completed phase I trial. IntraBiotics is now in two prophylaxis trials: phase III for intestinal VREF (which leaks into the body during chemotherapy), and phase II for nasal MRSA (which can lead to post-surgical infections).

Ramoplanin is not directly comparable to new drugs for systemic gram-positive infections such as Synercid (recently approved) and ZYVOX (linezolid; positive phase III results). “Topicals [such as ramoplanin] can’t do anything about bacteremia, and that’s the major use for antibiotics,” says Fred Tenover, chief of the nosocomial pathogen branch at the Centers for Disease Control (Bethesda, Maryland). But Kelley says that a prophylactic is used far more often than a last-resort treatment like Synercid, and so is financially important. The danger with frequent usage is, of course, resistance. “Typically, you get resistance development in anything from 1 to 20 years,” says Tenover. “There haven’t been very many that have made it to 20 years, with the exception of vancomycin.”

IntraBiotics hopes that new targets and no *in vitro* resistance mean that time is on their side. Locksley says the new drugs are important, but to slow the cycle of resistance “there is no easy road — you need a lot of education.” The solution is less antibiotics — in everything from animal feed and house-cleaning agents, to useless prescriptions for viral infections. “It’s a misunderstanding of the public to think that the world is a sterile place,” says Locksley. “They must realize that normal flora is a good thing.” Like everyone else, IntraBiotics will have to fight the idea that more is better.

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Table 1

Other companies developing antimicrobial peptides.

Company	Technology and status of trials
Magainin Pharmaceuticals Inc.	New drug application for magainin as treatment for infected foot ulcers in diabetic patients refused by FDA.
Periodontix Inc.	Histatins from human saliva in phase II for gingivitis and phase I/II for oral candidiasis.
Applied Microbiology, Inc.	Stalled in early trials with nisin, now selling Lite Bites® nutrition bars in partnership with the QVC television network.
Micrologix Biotech Inc.	In phase II for the prevention of central venous catheter-related bloodstream infection.
Biosource Technologies	Preclinical, using plant viruses to produce material. Have option on new peptide macrocycle from primates.