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Innovations

Quorex Pharmaceuticals, Inc.

Taking the Bull by the Horns

Antibiotic resistance has been a steadily growing crisis for decades. Antibiotic-insensitive strains of bacteria were seen as early as 1945, just two years after drug companies started mass producing penicillin. Since the early 1990s, there have been several reports of bacteria in patient samples that resist all antibiotic drugs available.

"There's no way around the fact that bacterium exposed to any drug, if it slows their replication or impairs their survival, will develop resistance," states Jeffrey L. Stein, Ph.D., Executive Vice President and Cofounder of Quorex Pharmaceuticals, Inc. He continues, "One way that we can slow [a microbe's] ability to develop resistance is to come up with completely novel molecules that they have not seen before."

A potential weakness of antibiotics as a general class of therapeutics is that almost all of those currently available are natural products or semisynthetic derivatives of natural products. While that may not seem problematic, it is. For example, penicillin is extracted from the soil microbe *Penicillium*, which secretes penicillin in order to eliminate competing microbes. *Penicillium* has coexisted and coevolved with other microbes in the environment, allowing for neighboring microbes to acquire resistance to its penicillin. At the time of its discovery, clinically pathogenic bacteria were penicillin sensitive, but given that a resistance mechanism against penicillin already existed in nature, it was only a matter of time before the infectious microbes acquired the mechanism as well.

The current approach at Quorex Pharmaceuticals, Inc. is to develop novel molecules that, unlike penicillin and most other antiinfectives, are not found in nature and can specifically bind to a highly conserved active site of an essential target in a broad spectrum of bacteria and fungi. In the fall of 2002, Quorex acquired the bioinformatics company Protein Vision, Inc. Protein Vision has trademarked technology based on a series of proprietary algorithms that allow recognition and annotation of unknown genes and three-dimensional modeling and functional analysis of the proteins they encode. By coupling the capabilities of Protein Vision with the company's established structure-based Accelerated Drug Discovery System (ADDS), Quorex has an efficient and rapid approach to identifying novel targets and synthesizing inhibitors with improved potency and selectivity.

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Quorex was initially incorporated as Quorum Pharmaceuticals in February of 1999 and opened its laboratories in San Diego, California later that year. Cofounders Jeffrey Stein, Ph.D. and Robert L. Robb started their antiinfective company based on the discovery of the autoinducer-2 (AI-2) pathway first identified in *Vibrio harveyi* by Bonnie Bassler, Ph.D. at Princeton. Bassler showed that the AI-2 molecule is secreted out of the cell, and at low cell densities this compound produces no detectable effect. However, at high cell densities the secreted AI-2 molecule is subsequently taken up by a neighboring cell, in which it acts as a transcription factor, upregulating pathogenic genes such as the proteases and elastases characteristic of bacterial infections. This apparent "sensing" of the bacteria at high concentrations is referred to as quorum sensing. Bassler and her colleague Michael Surette subsequently showed that upwards of 30 bacteria produce an autoinducer identical or highly similar to *V. harveyi*'s AI-2. This list included the clinically pathogenic bacteria such as *Escherichia coli*, *Salmonella typhimurium*, and *Staphylococcus aureus*. Bassler shared the finding of AI-2 with her friend and former colleague Jeffrey Stein, who then turned this discovery into the start-up platform for a company. In order to avoid blurring the boundaries between her academic pursuits and the pursuits of Quorex Pharmaceuticals, Bassler decided not to have a role in the company, aside from serving as scientific advisor.

Quorex is a small biotech of 48 employees and since 1999 has progressed in tackling the universally enormous antibiotic problem. "Of all the therapeutic areas, the highest failure rate is in antiinfectives in the discovery phase," claims Stein. This is because the research demands the discovery of a single inhibitory molecule to target slightly different versions of a target—a single antibiotic for a spectrum of bacteria. The pursuit of a new generation of antibiotics has been ongoing. Many large pharmaceuticals have discontinued this area of research due to failures in finding the elusive novel molecule capable of inhibiting a highly conserved broad-spectrum target. This is how Quorex surmised that shutting down the conserved AI-2 quorum sensing mechanism found in several species of bacteria could prove successful. Unfortunately, AI-2 is not essential for bacterial growth. Thus, any inhibitor of AI-2 would potentially shut down the expression of the pathogenic genes, but it would not kill the bacteria. The end result would be a bacteriostatic antibiotic rather than one that is bacteriocidal. Bacteriostatic antibiotics, such as tetracyclines (including doxycycline and minocycline) and

erythromycins (including Biaxin and Azithromycin), keep bacteria from multiplying but do not remove the invading bacteria. These bacteriostatic agents can work with good efficacy for an infected patient with a strong immune system. However, for an immune-deficient patient or one with a high degree of infection, a bacteriocidal antibiotic is preferred. As a small company wanting to secure itself for the long term, Quorex decided to aggressively pursue a bacteriocidal antibiotic.

Thus, the AI-2 research is put on hold with the hope of a future return, and Quorex is currently focusing on the small molecule design for isolated targets found in a spectrum of bacteria. Using the Protein Vision technology, Quorex researchers have isolated gene targets found in the nosocomial (hospital-acquired) bacteria, including at least the drug-resistant forms of the gram-positive *Staphylococcus aureus*, *Streptococcus*, *Enterococcus*, and the gram-negative *Pseudomonas aeruginosa*. Once a conserved target is found in all of these strains, Quorex examines the detailed three-dimensional structure using homology modeling and protein folding predictions to ensure that these conserved targets by amino acid analysis are also conserved in the physical structure of the binding site. The inhibitors will be synthesized to bind to specific amino acid side chains; however, for proper efficacy the side chains must be similarly exposed in all bacteria for binding to occur.

Out of the thousands of potential targets rendered using the genomic search capabilities of Protein Vision, Quorex narrowed the list to approximately 24 potential targets that seemed amenable to a drug discovery effort. This list of 24 was then prioritized based on evidence from previous studies. Those targets that had previously qualified as good candidates were pursued first. Currently, Quorex is actively pursuing novel inhibitory molecules to the following three key targets: (1) the DNA gyrase subunit B, which dimerizes with subunit A to catalyze DNA supercoiling required for bacterial transcription; (2) the fabH gene encoding a ketoacyl synthase III that is essential to and is proposed to be responsible for initiation of fatty acid biosynthesis in bacteria; and (3) the DNA ligase subunit A, which is essential for bacterial transcription.

Interestingly, the currently prescribed Ciprofloxacin targets the DNA gyrase A subunit. Ciprofloxacin, which gained widespread publicity as the antianthrax drug, carries a $6.5 billion market as the fifth generation of the fluoroquinolone antibiotics. The fluoroquinolones have proven to be quite successful against gram-negative bacterial infections with poor coverage of gram-positive pathogens. Unfortunately, Ciprofloxacin resistance exists, and in time its currently observed efficacy will wane.

As with most other antibiotics, the fluoroquinolones were derived from nature. They were found to have antiinfective effects and were subsequently prescribed before the mechanism of action was known. Therefore, if Quorex can design an inhibitor to a similar yet novel target site, DNA gyrase subunit B, using a more highly conserved target found in a broader spectrum of bacteria, an antibiotic can be rendered that has never stimulated a resistance mechanism in nature prior to its distribution. Quorex's theory is that this approach may engender a new class of antibiotics.

The broad-spectrum antibiotic candidate against DNA gyrase B is currently in animal studies, which are expected to be complete by late 2003. The fabH and the DNA ligase A candidates are following closely behind the first. While the three phases of FDA clinical trials still remain before any are marketable, animal studies for antibiotics are highly predictive of clinical trials. This is due to the fact that these antiinfectives are targeting bacteria whether they are harbored in animals or humans. With a potential for FDA fast track status, successful animal data could transition quickly into phase I trials by early 2004.

It may seem perplexing that the design of a compound that specifically binds to conserved bacterial residues is an approach that was only adopted in the last few years. Amazingly, most antibiotic discoveries have happened serendipitously from natural compounds. While this has proven to be effective, this method of discovery is rather parochial and has the potential of limiting the effectiveness of future antibiotics. As Stein points out, "Quorex is amongst the first companies to apply modern structure-based approaches to antibacterial drug discovery." It if was an easy drug discovery, clearly it wouldn't have taken so long for this obvious approach to be implemented. One can hope Quorex will find continued success.

***Chemistry & Biology* invites your comments on this topic. Please write to the editors at chembiol@cell.com.**

Nicole Ballew is a freelance science writer based in Lebanon, NH (nballew@hotmail.com).