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Innovations

Microbia

Engineering Microbial Network Biology

As its name implies, Microbia is in the business of bugs—bacteria and fungi, that is. This company dons the roles of both prosecution and advocate for all sorts of microbes in a three-pronged systems-based approach to developing novel drugs. From its headquarters in the Kendall Square technology haven of Cambridge, Massachusetts, Microbia's 73 employees are lead by a founding team of ex-Whitehead Institute fellows now supplemented with pharma execs from Pharmacia, Merck, and Sepracor. "The founders worked extensively in understanding the cellular networks involved in bacterial and fungal pathogenesis and have brought that expertise here," says John J. Talley, PhD, Vice President of Drug Discovery at Microbia. That comprehensive approach to understanding disease pathogenesis is at the heart of Microbia's drug design efficiency efforts.

"Industry has been seduced by tools like proteomics, genomics, and high-throughput chemistry, for example," explains Talley. "But few people know what to do with all the information." It's what Microbia is not doing that is so different. Instead of focusing on a particular pathway or target for its drug design efforts, the company is taking a more macroscopic view. "A target or pathway itself isn't so critical," adds Talley. "You have to look at the whole organism, not just the cell processes in isolation, to see what the opportunities are."

"The appeal of network biology is that you're focusing on the whole system," says Bart Henderson, Vice President of Business Development at Microbia. "Cutting a biological process up in pieces can lead you to losing sight of the whole system." Adds Talley, "What works for us is combining the biology, pharmacology, and chemistry involved in making great drugs."

Anti-Invasins Block Tissue Invasion

Using its systems philosophy, Microbia's lead program is its self-named "Anti-Invasin" drug discovery effort to develop a novel class of antifungal drug. "What we've done is exploit new links of physiologies to disease, including those that aren't evident in a petri dish," says Henderson.

"There is significant unmet need for antifungal therapeutics underscored by increased systemic infection prevalence rates and mortality figures in immunocompromised patients," says Henderson. With conventional drugs, he cites data showing 50%–75% mortality in patients following systemic *Aspergillus fumigatus* infection, an infection occurring during oncology and in neutropenic patients (patients with an unexplained fever), and a 40% mortality rate with the more prevalent *Candida albicans*.

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Microbia researchers have discovered that fungal cells can sense pH, cAMP, and osmolarity, among other environmental cues, and can change their state when conditions are right to transition from their customary benign yeast form into an invasive form to invade tissue and cause disease. The invasive form excretes enzymes, destroying tissues. "Our drugs block the transition to an invasive form, so once the immune system recovers, you are perfectly competent to clear the infection," says Talley. Microbia designed a multiplex, high-throughput gene reporter screen to look for compounds that will block invasion. So far, the company has identified several Anti-Invasin classes with in vitro efficacy. "And we're enthused to say we have validated the approach in vivo in animal studies," adds Henderson.

"One of the banes of antifungal drug discovery is that it has been difficult to find specific fungicidal or -static targets not shared by human cells," says Henderson. The company hopes the novel mechanism of attacking these infectious pathogens will translate into limited cross-resistance with other antifungals too.

Microbia expects the Anti-Invasin program to enter human clinical testing in 2004. Its targeted use is in immunocompromised populations such as oncology, transplant, and HIV patients and in the ICU. These patients often have multiple indwelling lines such as catheters, which are notorious pathways for infection. According to Henderson, the exciting opportunity related to Anti-Invasin antifungals is their potential use alone or in combination with conventional therapies to enhance efficacy and drive mortality rates down. He also adds that there is another market opportunity with prophylactic therapy in high-risk, immunocompromised patients.

Other nonsystemic fungal infections, such as vaginal, skin, and nail infection, are mostly well served by current therapies. "We intend to pursue these indications only as far as treatment for recurrent infections that may be refractory or resistant to traditional drugs," says Henderson.

"With our Anti-Invasin program, we now have a biological proof of principle that this is a novel way to treat mammals," says Talley.

Anti-Biofilm Therapeutics

"The story line with our anti-biofilm strategy is not dissimilar to the Anti-Invasins," according to Peter M. Hecht, PhD, Microbia cofounder and CEO. "We use the same systems approach using our understanding of

the network biology underlying disease with great systems-based chemistry and pharmacology to attack these new mechanisms." In this case, Microbia is developing a novel class of antibacterial drugs.

"The problem we're after is intrinsic antibiotic resistance mechanisms," explains Hecht. "The more commonly discussed form is acquired resistance: the genetic changes in the organism that make it resistant to antibiotic use." Instead, Microbia is targeting physiological changes that microorganisms undergo when under attack. These windows into the biological networks that underlie this problem come from studying biofilms. When bacteria are out in the free-floating phase, they are floating as single cells and are sensitive to antibiotics. "But a substantial part of bacterial life involves being hunkered down onto surfaces and when threatened, activating a series of physiological changes making them up to 1000-fold resistant to antibiotics," says Hecht. A potential link between biofilm production and chronic otitis media (middle ear) infection was recently highlighted in the April 3, 2002 issue of the *Journal of the American Medical Association*. "What we've done is to understand the biological network that underlies that physiological shift and then apply our systems approach to simultaneously target that whole network at once with systems chemistry to best block the process of intrinsic resistance."

In the course of characterizing that network, Microbia researchers discovered critical elements shared between intrinsic resistance and acquired resistance, such as that seen in methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. "That broadens the application utility of our therapeutics because we can use these in combination with other antibiotics to restore sensitivity, broadening the spectrum of these important agents that have become constrained by acquired resistance," says Hecht. The company has already presented in vivo data showing that its lead anti-biofilm therapeutic, MM2137008, restores the efficacy of oxacillin against *S. aureus* biofilms. A similar potentiation effect has been shown with MM2137008 and vancomycin.

The market opportunities for Microbia's anti-biofilm therapies are targeted against hard-to-treat or recurring infections in which intrinsic resistance mechanisms play an important role. These include pneumonia, osteomyelitis (acute or chronic inflammation of the bone), skin and soft tissue injury, otitis media, and nosocomial or hospital-originating bloodstream infections like coagulase-negative *Staphylococcus* and *Enterococcus* species, which both tote a 20%–30% mortality burden among immunocompromised patients. "The impact for anti-biofilms would be to reduce hospital stays and mortality," says Henderson. Another application is for treatment and prophylaxis of medical device infections. Infected orthopedic implants, though uncommon, require removal and reimplantation. Vascular access devices such as indwelling catheters have 15% infection rates. And *Pseudomonas* infection can be a problem with long-wear contact lenses.

Studies on medical device materials have borne out anti-biofilm efficacy. When implantable devices or materials such as cobalt chromium, the common material for hip implants, and silicone, used in vascular access catheters, were coated with the anti-biofilm therapy MM2137008, *S. aureus* biofilm formation was inhibited in a dose-dependent way.

Bacteria Minifactories and Green Chemistry

Paradoxically, when Microbia is not trying to find new ways to block or kill microbes, it is busy boosting their growth and production efficiency. "This last part of our program, the precision engineering technology, is not a drug discovery program, but it is fundamental for our business," says Henderson of Microbia's designer microbe production technology. "We're using the same approach for engineering the regulatory circuitry in microbes to enhance production of pharmaceutical and fine chemicals and to synthesize novel chemicals for our partners." The underlying goal is to improve yields and the manufacturing process for these agents. In the February 2003 issue of *Nature Biotechnology*, Microbia scientists described one of their novel ways to identify genes required for the production of industrial molecules produced in microbes.

By mapping the network of pathways governing bacterial physiology, Microbia's engineering program efficiently up- and downregulates pathways involved in production. "Our approach is to precision engineer bacterial regulatory networks and apply it to these types of products to improve productivity in a short period of time, without the deleterious mutations that come with traditional methods," explains Henderson. This approach is taking the company into pharmaceutical and fine chemical manufacturing and also to the frontier of synthesizing chemicals via "green chemistry" instead of traditional petroleum-based chemistry.

Microbia's first precision engineering partnership, announced in September 2002, is with Teva Pharmaceuticals. Other partnerships will be announced later in the year. The company is using this program to fund its own drug discovery efforts," explains Hecht. "It is a way for us to use the same systems approach that underlies microbial physiology," he says. "In this case, instead of crippling the microbes, we're making them into better minifactories to help our partners make money and generate cash for us to fund drug discovery."

"Five years from now, we'll consider our most significant milestone the fusion of network biology, systems chemistry, and drug pharmacology, " says Hecht. Adds Talley, "Our vision is to integrate those three to make a successful organization that loves to make drugs."

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

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