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Innovations

Kosan Biosciences

Better Chemistry through Genetics

"I call it chemo-bio-chemosynthesis," says David C. Myles, Executive Director, Chemistry, at Kosan Biosciences, describing a triune production strategy for novel polyketides, a source of pharmaceuticals found in nature. Hayward, California-based Kosan is on a mission to improve existing polyketides and to develop new polyketide analogs as part of its drug development program.

Polyketides are not new. About 10,000 polyketides have been isolated, mainly in soil microorganisms, from which approximately 50 commercial pharmaceutical products, including antibiotics, anticancer drugs, and immunosuppressants, have been derived. What is new is how Kosan is building on the inherent biological activities found in polyketides to make better drug candidates.

Fundamental to Kosan's efforts is the structure of the polyketide biosynthesis enzymes, polyketide synthases (PKS). By manipulating the genes encoding PKS enzymes, the type, order, and number of PKS enzymes is altered. The end result is to make specific and, hopefully, medically relevant improvements to known polyketides or novel polyketides altogether.

Chemobiosynthesis over Combichem

"What we do is 'chemistry by genetics,'" says Leonard Katz, Vice President, Biological Sciences at Kosan. One strategy is to transfer the genetic instructions for making a polyketide out of its natural source, where it is usually produced in small quantities, into another more productive microorganism. Kosan's favored biological workhorse is *Streptomyces coelicolor* with efforts into developing *E. coli* as a model organism now quickly ramping up. "A major advantage of moving the genes into *E. coli* is the shorter life cycle compared with soil microorganisms," says Daniel V. Santi, MD, PhD, Kosan's CEO. Kosan is pursuing the PKS biosynthetic route in *E. coli* now.

Gene manipulation and chemobiosynthesis complete the Kosan technology platform. Through PKS gene manipulation, Kosan adds reactive sites to polyketides with previously chemically dead sites not amenable to chemical manipulation. "The highly functionalized nature of polyketides means that as you assemble the molecules chemically, you may also create stereochemistry," Myles says to explain why applying combinatorial methods is difficult with polyketides. "This way we give ourselves an opportunity to do chemistry by first doing genetics," says Katz.

Kosan's approach to polyketide chemobiosynthesis comes in two flavors. One involves a chemical phase where a small molecule is synthesized that mimics an intermediate in the biosynthesis of a known polyketide. The small molecule is first fed to a genetically modified organism. "The result of that fermentation process is an unnatural natural product," says Myles. "We then take that product and use the chemical handle we've engineered into the polyketide—the legacy of the small molecule fed into the fermentation process—and modify it chemically to achieve any of the properties we're after," he says. Clinically, Kosan is targeting this approach squarely at the anti-infective and anticancer markets, where drug resistance is a concern. "We're starting with a proven drug with known pharmacological qualities where cells have become resistant and building something with enhanced activity," adds Katz.

"The technology itself is amenable to combinatorial biosynthesis, where by mixing and matching these genes you could create entirely new libraries of polyketides." –Daniel V. Santi, Kosan cofounder and CEO

The other, more recently developed approach is the chemo-bio-chemosynthetic route for producing novel polyketides. "This really takes chemobiosynthesis to the next level," says Myles, describing the process of manipulating PKS genes to synthesize small fragments of polyketides that are readily amenable to chemical modification and then assembling those fragments to make large complex polyketides.

Mimicking Natural Modular Chemistry

Kosan got its start—and its name—in 1995 from cofounders Santi and Chaitan Khosla, PhD, Professor of Chemical Engineering, Chemistry, and Biochemistry at Stanford University. Some of the early knowledge was contributed by Leonard Katz, then at Abbott Laboratories, about a natural system of modular chemistry for creating complex molecules.

"The technology itself is amenable to combinatorial biosynthesis, where by mixing and matching these genes you could create entirely new libraries of polyketides," says Santi. Yet early on, Khosla and Santi realized that the company's technology would have added results in the pharma business, scientifically and otherwise, by modifying polyketide drugs already validated in terms of their potential as pharmaceuticals.

They set out on their quest to modify these drugs either in terms of changing their properties to improve efficacy or in the production process itself, where yields could be boosted significantly.

High-Value Pharmaceutical Targets

Kosan is focused fairly exclusively on a few high-value pharmaceutical targets. About 15%–20% of its research budget is devoted to furthering the underlying technology. Its lead program includes the epothilones, polyketide products that have a mechanism identical to Taxol but with efficacy on Taxol-resistant cancer cells. Kosan also has a collabo-

rative project with Johnson & Johnson Pharmaceutical Research & Development, LLC, developing ketolides, a next-generation antibiotic. Kosan is also joining efforts with Meiji Seika Kaisha, Ltd, for antibiotic drug development. Two other anticancer programs include production of discodermolide, a compound with cancer-fighting properties found in an unculturable microorganism in sea sponges, and developing geldanamycin polyketides to bind to a heat-shock protein called Hsp90 and deplete cells of signal transduction proteins.

Lead Agent in Phase I Testing

The company's lead agent, KOS-862 (Epothilone D), is a tubulin-stabilizing compound that inhibits cancer cell division. "This is the first small molecule in a clinical trial that was produced in a heterologous host," says Katz. He adds that it also represents the largest set of genes transferred to another organism and expressed.

KOS-862 was synthesized in the laboratory of Samuel Danishefsky, PhD, Department of Chemistry, Columbia University, and Director of the Laboratory for Bioorganic Chemistry at Memorial Sloan-Kettering Cancer Center (MSKCC). "He is the man who first synthesized it by total chemical synthesis," says Santi of the drug Danishefsky referred to as EpoD in his own lab and one of several 12,13 desoxy epothilones synthesized and evaluated by MSKCC scientists. "We came upon these compounds through chemical synthesis, following our perception that the epoxide linkages of the A and B epothilones might be very damaging and not critical for activity," he says. Accordingly, his synthesis team deleted the epoxides and got to the D series with far better biological profiles in mice than the more common epothilones A and B.

KOS-862 is in two ongoing phase I trials, with a third just starting at MSKCC. All of these phase I trials are in patients with advanced solid tumor malignancies with unsuccessful treatment on other standard therapies. Early results suggest the drug is well tolerated, though an optimum therapeutic dose has yet to be determined. Kosan is targeting the end of 2002/early 2003 for start of phase II efficacy trials.

Kosan has an ongoing agreement with MSKCC directed toward continuing analog synthesis, giving them access to new chemistries and new synthetic routes. "One of the most important goals of my lab is to find new epothilones with valuable activities," says Danishefsky, who is also a member of Kosan's Scientific Advisory Board. He adds, "If, as we expect to be the case, a clear alternative to epothilone D (i.e., a 'backup' compound) would come forth, another goal would be the synthesis of that compound by purely chemical means, if need be."

According to Danishefsky, the epothilone field serves to underscore the power of focused chemical synthesis. As an example of this, a new chemical strategy to synthesize many novel epothilones has just been published by the Sloan-Kettering group in the *Journal of the American Chemical Society*. "In this new synthesis, we used olefin metathesis to create a novel 10,11 dehydroepothilone D, which Kosan had discovered earlier and termed epothilone 490," says Danishefsky. "Our total synthesis strategy makes it possible to generate totally novel epothilone analogs in a highly convergent way."

In Limited but Good Company

Kosan is one of just a small group of companies focused exclusively on polyketide drug development and discovery, which includes Biotica Technology, Ltd, a 20-person spinoff from the University of Cambridge, England. "We are watching the progress of Kosan's epothilone D with some interest, as, if approved, it would be the first small molecule drug developed from the start to be produced by genetic engineering," says Simon Turner, PhD, Biotica CEO. Founded on the science of Cambridge researchers Peter Leadlay and Jim Staunton, Biotica has yet to identify a lead agent for human testing, but its most advanced discovery projects include an angiogenesis inhibitor and an antiproliferative agent. And Galilaeus Oy in Finland is working on engineering novel polyketide analogs such as the anthracycline anticancer agents.

In the epothilone field, though, Kosan's KOS-862 is in the development company of compounds both in phase II testing from Novartis and Bristol Myers Squibb. "BMS has had a number of responses in different tumors with their epothilone," says Santi. "We'll use those results to guide our phase II trials."

Combinatorial Polyketide Libraries

In June 2002, Kosan was awarded a $2 million Advanced Technology Program grant from the National Institute of Standards and Technology to support what Katz calls "morphing" polyketide synthase genes by combinatorial biosynthesis. "This grant is to take the separate modules on the PKS genes and put them together so they'll talk to one another and create any molecule we wish by genetic engineering." Adds Myles, "Success in this area of morphing actually opens up the possibility of making combinatorial polyketide libraries," and opens with it an assortment and collection of potential drug candidates previously unavailable.

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

Alice A. McCarthy is a freelance science writer based in Magnolia, MA (alice@alicemccarthy.com).