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Innovations

Theravance

Medicines that Make a Difference™

Theravance believes in its mission statement so strongly that they have trademarked it. This South San Francisco-based company, intent on discovery and development of best-in-class blockbuster medicines, has a powerhouse in its Board of Directors, its scientific team, and its drug development candidates, all thanks to the concept of more is better. In Theravance language, this means multivalency.

Multivalency

"Multivalency is a philosophy within chemistry," according to Mathai Mammen, MD, a Theravance cofounder and Director of Medicinal Chemistry. Theravance is building on the concept of polyvalent entities described by George Whitesides, PhD, Harvard and MIT researcher and Theravance cofounder. These entities were polymers displaying multiple copies of the same ligand on their backbone. Each identical chemical moiety had the same function and bound to a defined target. "What we are doing is a bit different in that we are identifying different, well-defined binding sites on biological targets that have not been exploited before for various reasons," says Mammen. Theravance researchers then develop small molecule drug compounds using a bivalent or multivalent approach rather than using the large polyvalent constructs that were intriguing to company founders. "We are dialing in superior selectivity and specificity, " he says, "and in the process creating small molecules that will attach to two or more sites on a target."

"When I first heard about multivalency, I thought you might get nonspecific binding with the additional binding sites, but it is actually quite the opposite," explains Patrick Humphrey, PhD, DSc, Executive Vice President of Research at Theravance. "We get more specificity because the secondary binding site(s) is equally unique to the targeted protein(s) as the first."

"We do not do random screening," says Humphrey. "Instead, it is rational medicinal chemistry, where we know the target sites we are going after and are only creating molecules intended to bind in a better way to those sites." The company hopes that these improvements in selectivity and specificity will reduce unwanted side effects from nonspecific binding. "Improvement in potency and duration of action are added potential benefits," adds Humphrey.

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Bicoastal Roots

The seed idea for Theravance, now the corporate home to more than 200 employees, started years ago in academic labs working on the polyvalent concept. In two research institutes on opposite coasts, researchers John Griffin (Stanford) and Mathai Mammen (Harvard) were working on the idea, developed years earlier, that multiple ligands or drug targets bound together somehow provides advantageous binding specificity potency millions of fold higher than the ligands on their own. "That idea was developed on a polyvalent construct," explains Mammen, "and eventually enabled the initial round of financing that started the company, then called Advanced Medicine." Theravance opted for its name change about a year ago, and its technology focus is now on smaller constructs, like bivalent constructs.

Big Pharma Experience

It also helps Theravance's drug development efforts to have P. Roy Vagelos, MD, former Merck CEO and Board Chairman, as a cofounder and Chairman of the Board. In 1996, Vagelos immediately set about recruiting a number of highly experienced senior executives from big pharma. "We have really been functionally operational for about five years now," says CEO Rick Winningham, a former Bristol-Myers Squibb executive, who has been on board since late 2001. In 2001, Pat Humphrey, a 30-year Glaxo executive, assumed the top research position at Theravance, a company he describes as "a drug discovery powerhouse populated by dedicated drug hunters." Theravance's commercial development team is led by David Brinkley, Senior Vice President of Commercial Development, who joined the team in 2000 after leaving Pfizer, where he was the senior marketing executive for the Viagra product.

Validated Targets and Best-in-Class Medicines

"We have the insight of multivalency applied to validated targets, and we do it with people who have a great deal of both passion and experience in the industry, " says Winningham. Researchers start by focusing on biological mechanisms known to have yielded successful medicines in the past. "We know that if we affect that target, that biological mechanism, a response will occur providing therapeutic benefit." With multivalency, Theravance hopes to avoid some of the problems associated with earlier medications, such as unwanted side effects and inadequate potency or duration of action. "All of those shortcomings with existing medicines provide us with opportunity," Winningham says.

"With multivalency, we're able to improve on potency, selectivity, and

duration of action: the three main areas we focus on, " says Brinkley. "We look at markets that we feel are currently ill served by the market leader and could be significantly aided by a next-generation compound that has some improvement in one or more of those key features."

"Our objective is to go for best-in-class medications," explains Winningham. So it is not surprising that the company's first corporate alliance with a major pharma company, GlaxoSmithKline (GSK), is in the field of longer-acting β_2-adrenoceptor agonists, one of the backbone treatments for chronic asthma and COPD. In January 2003, the companies announced their plan to pool compounds and resources to develop improvements to the current asthma blockbuster medications, Serevent (salmeterol) and Advair (combination salmeterol/fluticasone therapy), both manufactured by GSK. "In drug class after drug class, the second- or third-generation drug has done substantially better than the first," says Brinkley, "and there is a lot of benefit to be brought to patients." Not incidentally, this translates into a lot of money to be made for the company that does it.

Antibiotics in the Lead

"It is clear in practice that multivalency delivers drugable molecules at an impressive rate," says Humphrey. Theravance has advanced six compounds to drug development candidates, all discovered in the last three years. The lead candidate, Arbelic (TD-6424 for injection), an intravenous antibiotic, entered phase II trials in April 2003.

"An important facet of multivalency is its potential to deliver multifunctionality," says Humphrey. Arbelic is just one example of several Theravance projects where the drug is designed to bind to two or more fundamentally distinct protein targets. "Providing the targets are appropriate to allow binding to both with a single molecule, you get bifunctionality," says Humphrey.

Arbelic appears to have the classic glycopeptide or vancomycin-type activity, inhibiting cell wall synthesis. "The unique twist is that this molecule also penetrates into the bacterial cell membrane and inhibits phospholipid synthesis, which is a novel mechanism of action that has not been demonstrated with any other clinically used antiinfective," says Ken Pitzer, DVM, Senior Director of Commercial Development. Because of the drug's multiple mechanisms of action, it appears to be rapidly bactericidal against gram-positive organisms, especially methicillin-resistant Staphylococcus aureus (MRSA) and other similar resistant strains. "The hope is that by having a rapidly bactericidal drug, patients will not have to be on therapy as long as they traditionally are with drugs like vancomycin," adds Brinkley. He hopes that faster infection resolution with multiple drug actions will reduce the likelihood of resistance developing or at least slow it down.

Longer-Acting β-Agonists

Behind Arbelic is the joint Theravance/GSK longer-acting β_2-adrenoceptor agonist program. "When we first approached the program, we did so almost out of a sense of curiosity to see how mutivalency could address signaling motifs in 7-transmembrane G-protein-coupled receptors," explains Edmund Moran, PhD, Vice President of Medicinal Chemistry at Theravance. "The β_2-adrenoceptor, a 7-transmembrane receptor, is very well described in the literature with two well-known drugs, the rescue bronchodilator drug albuterol (an agonist for the receptor) and salmeterol (a long-acting version of that, now a key component in the Advair product), available to stimulate it."

By the late 1990s, several studies began to suggest that receptor dimerization played an important role in the signaling of the β_2 adrenoceptor. "We attempted to capture this receptor dimerization motif with a dimeric molecule capable of binding to adjacent interreceptor agonist binding sites," says Moran. "This search led us to eventually discover a series of small molecules that appeared to bind to two sites within the β receptor rather than binding in an interreceptor fashion. We were looking for a molecule like this to perhaps lead to a once-a-day inhaled medicine." Salmeterol currently requires twice-daily dosing. The result of that agonist discovery program are the compounds now in development with GSK. One of the lead candidates from that program, now in phase I testing, is on track for phase II by year end. Another is poised to initiate phase I testing later this year.

Future Programs

Theravance has another respiratory program in anticholinergic bronchodilators, the long-acting inhaled muscarinic antagonists. "Through multivalency, we have managed to make a wide range of molecules to bind with the five different types of muscarinic receptors with all sorts of activity patterns," says Mammen. "We use those selectivity patterns to our advantage to first understand, then target a variety of illnesses, including COPD and asthma." The company is developing muscarinic antagonists for overactive bladder as well. "There is a chance one of those drugs will be in phase I by year end also, " says Brinkley. Behind the respiratory projects, which also include an inhaled PDE4 inhibitor program, are an intravenous anesthetic and a gastric motility research effort.

"Multivalency continues to evolve," says Mammen. "It puts us down pathways of drug discovery that are not typical. We use multivalency not just because of the kind of compound that can come out the other end, but we treat it as a philosophy that generates lead structures for us that are fundamentally different."

When Vagelos joined the Theravance effort, he helped take a core scientific innovation in polyvalency and began translating it immediately into medical terms and drug development opportunities. "We learned to design forward-looking plans early on in our discovery phase to get these drugs to market," says Brinkley. Adding, as only as a senior marketing guy can, "Our aim is not just to get to the clinic with compounds. We want to get through it."

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

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