BY KIM RIBBINK

DR. SPIROS JAMAS

is leading **Enanta Pharmaceuticals** by tapping the company's primary strength in its **integration of chemistry and biology to tackle new targets and specific drug-development challenges** from all possible angles right from the start. He is relying on the hard-won lessons learned from his 11 years at the helm of Alpha-Beta Technologies, a biotech company he founded just out of graduate school.

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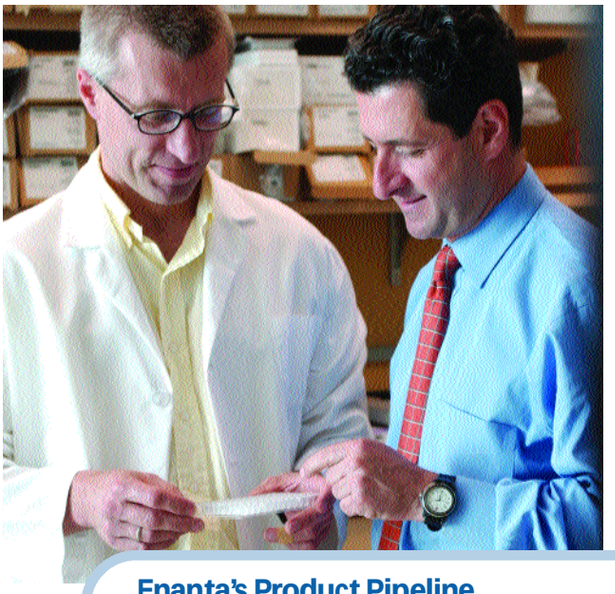

cal Reaction

Spiros Jamas, Ph.D., is not one for half measures. Given his background and academic experience, that's hardly surprising. While at Massachusetts Institute of Technology in the 1980s, where Dr. Jamas earned a master of science in food science and technology and a doctor of science degree in biotechnology, he was part of the burgeoning Boston-based biotech and bioengineering movement.

"I was lucky to be at MIT at a time when there was a lot of stimulating activity in the area of biotechnology; several of my professors were involved in the formation of biotech companies or advising biotech companies," he says. "More specifically, with regard to my thesis, my advisor had received funding from a number of sources, including the U.S. Navy that were very interested in exploring both medical and industrial applications of carbohydrate polymers. I realized that we weren't just working on an academic research project but that there were also some very interesting commercial applications for this research."

Enthusiastic about the medical possibilities of his theoretical work while at MIT as a postdoctoral associate at the Laboratory of Applied Microbiology, Dr. Jamas decided to go into the private sector, and he hasn't looked back since. Dr. Jamas' entrepreneurial spirit and common-sense approach to business were fostered by his father, who was, Dr. Jamas says, an entrepreneur at heart.

He began his career by founding Alpha-Beta Technology Inc., which he led as president, CEO, and director for 11 years until the company wound up operations and sold its assets in 1999. His extensive experience in leading Alpha-Beta's scientific and business programs, directing operations, and spearheading funding made him a natural candidate to steer other emerging biotech companies. Twice he has been selected by venture capital investors and company founders to lead companies, first at Repair Inc. and then at Enanta Pharmaceuticals Inc., where Dr. Jamas has been president, CEO, and director since June 2001.

Dr. Jamas' entrepreneurial penchant for forging new ground is a good match for the emerging Enanta, which has a strong commitment to state-of-the-art and innovative chemistries that transcend traditional medicinal chemistry approaches in the use of the latest synthetic methodology, novel catalysts, and stereochemically controlled library synthesis. Enanta's mission is to accelerate drug discovery by focusing on transforming existing drugs, natural products, and biologically active peptide leads into small molecules with improved pharmacological properties.

The company's primary strength lies in its integration of chemistry and biology to tackle new targets and specific drug development problems from all possible angles right from the start. This comprehensive approach is expected to ultimately shorten the time between project inception and clinical trials.

The current focus of Enanta's medicinal chemistry program is directed toward the discovery of novel macrolide antibiotics, antivirals, and anti-inflammatory agents. The company uses its synthetic capabilities to modify existing macrolide natural products to overcome bacterial resistance and to improve their biological profiles.

For Dr. Jamas, much of the attraction to organizations such as Enanta is the new methodologies and techniques that young companies employ, as well as the people who are attracted to such companies.

"The science is always cutting edge, and

Enanta's Product Pipeline

Lead Candidate	Indication	Market	Status
EP-13420 Macrolide	Respiratory Tract Infection	$1 Billion	IND 2004
EP-13159 Macrolide	Nosocomial Infections	$400 Million	IND 2004
Cyclosporines	Asthma, Psoriasis, Transplantation	$1.2 Billion	Preclinical
Protease Inhibitors	Chronic Hepatitis C	$2 Billion	Preclinical

Source: Enanta Pharmaceuticals Inc., Watertown, Mass. For more information, visit enanta.com.

Novel Chemistry

ENANTA WAS FOUNDED ON PEPTIDE MORPHING, DEVELOPED BY GREGORY VERDINE, A PROFESSOR OF CHEMISTRY AT HARVARD UNIVERSITY.

Peptide morphing is a unique technology approach to the transformation of biologically active peptides into nonpeptide small-molecule drugs that take advantage of advances in modern synthetic methods. Advances in genomics and biotech research have led scientists to discover many peptides that interact specifically with selective targets, including receptors, proteins, and enzymes. One advantage of peptides is their shape, as well as their chemical structure, giving them their specificity to bind to a very specific receptor and not to other receptors. The disadvantage to peptides as drug targets, however, is that they typically are degraded very rapidly in the body, which means they would need repeated administration. Also, they cannot be delivered orally because peptides won't survive the acidic environment in the stomach or be absorbed through the intestine.

ONE KEY AREA IN WHICH THE COMPANY IS APPLYING ITS CHEMISTRY SYNTHESIS TECHNOLOGIES IS IN THE MACROLIDE ANTIBIOTIC AREA. The first macrolide developed about 50 years ago was erythromycin A, which initially was approved for use in patients with penicillin allergies and later had broader uses. Existing macrolide compounds, such as erythromycin A and its derivatives, are 14-membered ring antibiotics that often are accompanied by poor oral bioavailability, multiple daily dosing requirements, and adverse gastrointestinal side effects such as nausea or cramping. More importantly, key pathogens such as *Streptococci pneumoniae* are developing increasing resistance to currently available macrolide antibiotics.

Spiros Jamas, Ph.D., president, CEO, and director, of Enanta explains that the company is trying to take some of the lessons learned with regard to natural products, such as erythromycin A, and use those attributes to develop better drugs or compounds that will overcome the shortcomings of existing drugs and fill unmet medical needs in large therapeutic markets. "We have a lead macrolide compound that we're pushing forward to an IND and into Phase I next year to treat community-acquired respiratory tract infections such as pneumonia, bronchitis, and sinusitis," he says. "This compound overcomes the macrolide resistance mechanisms of streptococci, the main pathogen involved in these infections. Not only is the compound very potent at overcoming this resistance, it also has a pharmacokinetic profile that is unprecedented in this area — our product has a half life in dogs of about 11 hours with oral dosing compared with the competition in this area, which is superior to competing drugs in head-to-head studies. We think this will result in lower doses, even once a day dosing."

ANOTHER KEY FIELD OF RESEARCH FOR ENANTA IS IMMUNOLOGY. The company has developed a class of proprietary cyclosporine A analogs with improved toxicity profiles. These compounds can be delivered topically to the target organ (lung, skin, or colon), exert a potent local anti-inflammatory effect, and are inactivated upon systemic absorption thus limiting their toxicity. "Through market assessment we concluded that if we could develop a cyclosporine analog that retained the same anti-inflammatory activities as cyclosporine but had reduced kidney toxicity this could open up significant new indications," he says. "We have developed a proprietary catalyzed chemistry process that allows us to modify cyclosporine in a way that hasn't been possible before. And we believe that by changing how cyclosporine is metabolized in the body, we could thereby reduce kidney toxicity."

Enanta started with *in vitro* assays before moving into animal models. Recent research from Enanta into its cyclosporine program shows the altered biotransformation of the compounds results in a significant reduction of kidney toxicity in rats, while maintaining efficacy.

developing new therapies for disease is a great goal to be working toward," he says. "These are exciting times, and I have the opportunity to work with really bright and experienced people who are helping to drive Enanta's business plan."

Engineering a Career

While in college in the United Kingdom studying chemical engineering, the field of biochemical engineering began to emerge and Dr. Jamas found himself drawn more toward this arena as well as biotechnology.

"Biochemical engineering was a very new field, we were learning to grow organisms or bacteria to produce specific products or chemicals; the possibilities seemed endless in terms of using biology to produce complex chemicals," Dr. Jamas says. "The emergence of biotechnology provided a lot more versatility to chemical engineering."

Toward the end of Dr. Jamas' thesis work at MIT, he met Joyce Czop, an immunologist from Brigham and Woman's Hospital in Boston, which is a nonprofit teaching affiliate of Harvard Medical School. His colleague had isolated a receptor on human white blood cells, and more specifically on human neutrophils, which was involved in triggering inflammatory responses.

Dr. Jamas explains: "After we started working together we realized that by changing the structure of the glucan of the natural carbohydrate ligand to the receptor, we could change the inflammatory responses that were triggered in white blood cells."

Glucans are present on the cell wall of all fungal cells. Over time, the human immune system has evolved an ability to defend itself against fungal infections by recognizing that a glucan is present. The receptors that evolved in white blood cells, when triggered, stimulate what today is called innate immunity, which is the nonspecific immune responses that are triggered by phagocytic cells.

The two scientists reasoned that they could use glucans to either stimulate or inhibit specific immune responses to fight fungal and bacterial infections.

But taking a scientific observation from the

lab and trying to push the theory into a formal drug development process was, Dr. Jamas says, a tremendous challenge and a learning experience. The new science also was tricky in terms of formulating data for regulatory authorities since it was previously untested.

"We had to develop the manufacturing processes from scratch, and we had to develop the methods to analyze and control the quality of the product," he explains.

Alpha-Beta, which began operations in 1988, closed its doors in 1999 after its lead product failed in Phase III clinical trials. That product, Betafectin, was a glucan to treat infections following gastrointestinal surgery. Betafectin became Alpha-Beta's chief focus after receiving encouraging Phase I and Phase IIa data.

Despite the disappointment of having his company fold, Dr. Jamas is very proud of what he and his team accomplished at Alpha-Beta.

"In hindsight, the team achieved some tremendous milestones," he says. "We were a small and dedicated group focused on developing a product that could have had tremendous therapeutic potential."

He notes that another company has sublicensed the patent portfolio and is continuing work on Betafectin.

Enanta's Business Strategy

Macrolide antibiotic
- Enanta to fund development through Phase I/II
- Partner with global pharma partner
- Retain rights to specialty indications

Cyclosporine program
- Partner for inhaled asthma indication
- Codevelop topical psoriasis indication
- Codevelop systemic analogs for rheumatoid arthritis, transplantation

Drug discovery collaborations
- Fully funded deals
- Enanta chemistry and partners biology

Source: Enanta Pharmaceuticals Inc., Watertown, Mass.
For more information, visit enanta.com.

"Perhaps one of the main lessons I took with me from Alpha-Beta was that, because of the inherent risks of drug development, where only a small percentage of products that go into clinical development ever get approved, it is important to have a pipeline of products to mitigate the risk," he says.

Following an Entrepreneurial Path

SPIROS JAMAS — RESUME

2001-PRESENT. President, CEO, and director, Enanta Pharmaceuticals Inc., Watertown, Mass.
1999-2001. President, CEO, and director, Repair Inc., Portland, Maine
1988-1999. President, CEO, director, founder, Alpha-Beta Technology Inc., Worcester, Mass.
1987-1988. Postdoctoral Associate, Laboratory of Applied Microbiology, Massachusetts Institute of Technology, Cambridge, Mass.

EDUCATION:
1983-1987. Doctor of Science in Biotechnology, Massachusetts Institute of Technology, Cambridge, Mass.
1981-1983. Master of Science in Food Science and Technology, Massachusetts Institute of Technology, Cambridge, Mass.
1978-1981. Bachelor of Science with Honors in Chemical Engineering, University of Manchester Institute of Science and Technology, Manchester, United Kingdom

AFFILIATIONS/ BOARDS OF DIRECTORS:
- Massachusetts Biotechnology Council
- Tissue Regeneration Inc.
- ALS-Therapy Development Foundation

Taking the Lead

In his current position at Enanta, which he assumed in 2001, Dr. Jamas gets his chance to oversee not only an innovative company with breakthrough technologies but one with a young pipeline of promising products. (See chart on page 41.) Dr. Jamas joined Enanta to lead the company's development of antibiotics and anti-inflammatory drugs. Enanta derived its name from a Greek word commonly used in chemistry — enantiomer, which is a mirror-image isomer. As Dr. Jamas explains, nature sometimes produces compounds of identical chemical structure with variances in their stereochemistry, which are mirror images of one another.

Already Enanta and Dr. Jamas appear to have the right chemistry. He has been responsible for raising $20 million of Enanta's $45 million in private equity financing, as well as engineering a strategic drug-development alliance with Chiron Corp. for hepatitis C therapeutics.

As the technical team was in place when Dr. Jamas joined Enanta, his role has been to shift the company's focus from discovery research to drug development. He is instrumental in generating the funding and capital to facilitate this next step in the company's growth and to provide direction and focus to Enanta's team of 35 chemists and biologists.

One of the big advantages of smaller, focused companies such as Enanta, Dr. Jamas says, is not having to go through the layers of committees and management meetings to get a project under way.

"With Enanta's current infrastructure, we are able to create a tremendous focus on a given project and then everyone understands what his or her role is and the impact on the company," he says.

The company is maintaining an open, yet targeted approach to its future, seeking early partnerships for some projects, links with big pharma later in the development stage for others, and even taking some niche products through the commercialization process on its own. (See chart on this page.)

One key partnership is with Chiron, for the discovery and development of small-molecule therapeutics for the treatment of the hepatitis C virus. Under the exclusive agreement, Enanta is applying its macrocyclic chemistry and medical chemistry expertise to the design and synthesis of compounds targeting key enzymes involved in the replication of the virus.

From Enanta's point of view, the agreement

was particularly beneficial because of Chiron's leadership position in the hepatitis C field. Chiron controls a number of patents to some of the key targets in hepatitis C, such as protease, which is an enzyme that has shown to be a very effective target in the HIV field. Dr. Jamas says, more recently, research has shown that inhibiting the same enzyme in hepatitis C could be an effective way to control infection in chronic hepatitis C patients, which is a major unmet medical need.

"We signed the deal with Chiron in August 2002 and in a very short time Enanta has delivered proprietary milestones to Chiron because our compounds have very potent activity against inhibiting the hepatitis C virus," he says. "To date, Enanta's scientists have developed multiple lead series with potent target activity, as well as activity against the virus in whole cell antiviral assays. Our near-term goals this year are to select a development candidate and then Chiron will be responsible for taking the candidate through the formal preclinical studies, an IND, and into the clinic."

Dr. Jamas says Enanta aims to retain rights to some of its products that focus on niche indications or hospital indications that can be served with a focused salesforce.

The company also will partner with larger companies for products that address broader indications.

"With the macrolide program, which is our lead program for community respiratory tract infections, our goal is to take the product through Phase II clinical studies ourselves, but then we would partner with a global pharma company that would be responsible for the Phase III development and registration worldwide," he says. "In the macrolide area, we have other lead compounds that address the more niche hospital-based markets and our interest would be to retain rights to these and drive these through the clinical development process, at least in the United States." ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.


SPIROS JAMAS

Inspired Choices

IN AN EXCLUSIVE INTERVIEW WITH PHARMAVOICE, SPIROS JAMAS, PH.D., TALKS ABOUT WHAT MOTIVATES HIM, AS WELL AS THE CHALLENGES FACING THE BIOTECH INDUSTRY.

CAN YOU TALK ABOUT SOME OF THE PEOPLE WHO HAVE INSPIRED YOU AND WHAT LED YOU TO THE LEADERSHIP POSITION YOU HOLD TODAY?

My father was my first inspiration. He was an entrepreneur at heart and was a tremendous influence for me, since he was very supportive and encouraging. He was always starting new businesses, many times from scratch, and this was a tremendous influence. Beyond that, in the biotech area, I am inspired by other successful biotech company leaders who have built up companies from scratch — Henri Termeer at Genzyme, Gabe Schmergel at Genetics Institute, and Wayne Hockmeyer at MedImmune. It's tremendous to see companies grow and survive through the ups and downs characteristic of our industry.

HOW DO YOU BELIEVE YOU INSPIRE OTHERS?

I'm an optimist and I try to convey that to the troops. It's important to be persistent and not leave any details out. But ultimately it's about having a team of individuals who have the same optimism and persistence around me. As difficult as certain situations can be, I don't let anyone around me feel that we're defeated or that things aren't going to work out.

WHAT IS IT ABOUT THE INDUSTRY THAT YOU FIND MOST INSPIRATIONAL?

I enjoy working with multidisciplinary teams. The ability to have access to a medical, biology, chemistry, and marketing perspective and assemble these influences into a R&D plan is inspirational. I am also inspired by what we've achieved at Enanta. The odds of a drug succeeding through development are fairly low but we're able to recruit talented, bright people who are willing to put in 12-hour days and build value. And that's gratifying.

WHAT DO YOU BELIEVE IS THE MOST PRESSING CHALLENGE THE INDUSTRY FACES?

The industry goes through capital crunches, as is happening right now. But that's a natural evolution and not every company is going to attract capital and be able to raise the capital to sustain its operations. Thus far, Enanta has been fortunate to raise enough capital to drive its priority R&D programs forward and create business-development opportunities. Another challenge is that the biotech industry has to find the right balance between how far it can take products and when to partner with big pharma. A biotech company has to forge alliances that allow it to retain enough value but also use the marketing and late-stage development expertise that big pharma has. I don't think we've reached a perfect balance yet where each party retains the piece of the value that is fair, but we are moving in the right direction.