Upping the Anti – Keeping Ahead of Antibiotic Resistance

Aimee Dingwell, News Editor at BioCentury Publications Inc, talks to Spiros Jamas, President and CEO of Enanta

Dr Spiros Jamas graduated from the University of Manchester Institute of Science and Technology, England, in 1981 with a BSc (Hons) in Chemical Engineering. He also holds a MSc in Food Science and Technology and a PhD in Biotechnology from the Massachusetts Institute of Technology. In 1988, Dr Jamas founded and served as President, CEO and Director of Alpha-Beta Technology, a company that developed medical applications of carbohydrates. During his tenure at Alpha-Beta, he was instrumental in raising $200 million through venture capital, as well as public financings. Dr Jamas has also directed two INDs, five Phase I, three Phase II, and two Phase III clinical trials, while concurrently acquiring another privately held biotechnology company. Following this, he held the position of President and CEO of Repair Inc, a biopharmaceutical company that developed sustained-release angiogenesis therapies for the repair of diseased organs and tissues. Dr Jamas has served as President and CEO of Enanta since the company's inception in 1999, providing scientific and business leadership.

Q The prevalence of antibacterial resistance seems to be rising, yet few new antibiotics have been approved in recent years. How dire is the situation and what is Enanta doing to address it?

A Drug resistance is continually increasing and the supply of new antibiotics has slowed. Resistance to antibiotics varies by geographic region and there is no doubt that clinically important species of bacteria such as Streptococci, one of the major causes of respiratory tract infections, have developed resistance to more than one antibiotic. A recent study completed by the Centers for Disease Control in the US concluded that by next year 40 per cent of Streptococci will be resistant to both penicillins and macrolides. Another potential concern is the spread of certain hospital pathogens to the community. Methicilin resistant *Staphylococcus aureus* (MRSA), an organism associated with surgical wound infections and bloodstream infections, was confined to hospitalised patients in the past, but MRSA is slowly spreading in the community. Enanta has discovered and is developing a new class of macrolide antibiotics commonly referred to as bridged ketolides, which have shown potent activity against the target resistant pathogens for respiratory tract infections and a superior pharmacologic profile to current generation macrolides in preclinical studies. To date, Enanta has generated multiple lead candidates that have exhibited potent *in vitro* and *in vivo* activity against such medically important pathogens as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Haemophilus influenzae* that is equal to or greater than that of currently marketed macrolides. Macrolides have been used successfully in this disease area since the introduction of the first macrolide, Erythromycin, in the 1950s. Resistance to existing macrolide antibiotics however, as well as pending patent expirations in 2005 of the two major macrolides, clarithromycin and azithromycin, and the approval in Europe of the first ketolide, Ketek, creates significant market opportunities for biopharmaceutical companies like Enanta.

Q Speaking of a dearth of new antibiotics, what do you think is limiting the development of new antibacterial compounds? Do you think that there will always be a need for industry to develop new or improved antibiotics?

A One cannot stop evolution, and as long as humans and bacteria are living in the same environment, there will be a need for new and improved antibiotics. The pace of antibiotic development has definitely slowed in recent years. This is partly due to the fact that many new antibacterial targets that have been discovered using genomic approaches turn out to be far from essential for the survival of the organism or are not selective enough, thus leading to adverse effects on other cells and further toxicity. Other reasons relate to an increased scrutiny by regulatory authorities on the criterion that will be acceptable to demonstrate safety and efficacy in the target patient population. This is leading to larger and hence longer and more costly clinical development programmes. The recent approvals in the US of a new fluoroquinolone, gemifloxacin, and in Europe of telithromycin (Ketek) for community acquired pneumonia caused by multi-drug resistant organisms, is proof that regulatory authorities understand the medical importance of approving new antibiotics that infectious disease experts can use to better treat patients.

Some would argue that spending research dollars to improve existing antibiotics, or create additional ones, is not cost effective. In fact, some are saying that pharmaceutical companies, once pioneers of antibacterial drug development, are getting out of the space due to market inefficiencies. How do you view the antibacterial market? Is there room for an antibacterial blockbuster or will the market remain fragmented?

The antibacterial market can be categorized into two broad segments, the hospital market and the community market, with the latter accounting for approximately 70 per cent of the US$25 billion worldwide antibiotic market. It is not surprising therefore, that there are a number of blockbuster antibiotics (greater than US$1 billion annual sales) targeting community-acquired infections. While some pharmaceutical companies have got out of antibacterial drug discovery, there are a number of major pharma companies that remain committed to this area and are funding significant internal programmes. From a small biotech company's perspective there is a clear opportunity to take a new antibiotic through Phase I or Phase II clinical development and then partner with a pharmaceutical company to leverage their strength in managing large Phase III studies and co-ordinated global registration and marketing activities.

One advantage we have is that traditional drug development has established a development path, including clinical study design, target patient populations and clinical endpoints, that is easy to follow and that regulatory authorities have experience with. A second important advantage is that many of the class-related liabilities of macrolides are already well understood and preclinical and clinical development packages can be tailored to address these important issues.

Having been at the helm of a few biotech companies, what attracted you to the drug morphing and peptide morphing technology platform?

Ensemble has expanded the scope of its initial technology, Peptide Morphing, to the application of cutting-edge stereospecific chemical synthesis to natural products and small molecules. Peptide Morphing was initially discovered in the laboratories of Professor Gregory L. Verdine at Harvard and licensed to Ensemble.

How are the technologies used in practice and how are they applied to generate new chemical entities?

Our approach is to use focused stereo-defined libraries guided by biologically active peptide templates to expedite the discovery of novel small molecule leads. The technology is based on chemical processes that introduce extensive spatial (three dimensional) diversity into the central molecular structure of a lead molecule, which in turn allows us to screen for the optimal pharmacological properties. Spatial diversity is achieved through the creation of replications of the molecule around chiral centres, also known as stereocenters. The optimal drug candidates may be identified in fewer design cycles because the high level of spatial and functional diversity introduced increases the chance in each cycle of identifying significantly improved products that retain favourable properties.

So the technologies use good old-fashioned chemistry to change the stereochemical properties of known compounds or biologically active peptides. Do you think that the value of chemistry has been lost on the current post-genomics drug development environment?

The value of chemistry in the post-genomics era has definitely not been lost. There is tremendous demand for novel and traditional medicinal chemistry capabilities to generate drug candidates for many new targets.

Hepatitis C virus is another disease for which developing drugs has proven tricky. What has been the hold up and how are Ensemble's compounds different to existing therapies?

According to industry research the hepatitis C virus (HCV) drug market will grow from $3.5 billion in 2002 to more than $9 billion in 2012. Presently, there is no vaccine or other means of preventing hepatitis C infection. Existing hepatitis C drugs used to treat the disease are effective in only 30 to 40 per cent of patients treated.

The main hindrance to drug development for hepatitis C has been the lack of a small animal model for assessing drug action. This problem has been addressed both by academic groups and private companies, which has resulted in a drastic improvement of the possibilities for in vivo research. The main obstacle has already been the difficulty of achieving viral replication in the laboratory both in cell culture and animal models. Our partner Chiron has established cell culture assay systems that can accurately assess a compound's ability to inhibit the growth of the hepatitis C virus. Ensemble has entered into a joint R&D and license agreement with Chiron involving the synthesis of compounds, structure-based drug design and testing of lead compounds in enzyme assays, whole cell assays and animal models. Macrocyclic chemistry expertise can thus be applied to the design and synthesis of compounds targeting key enzymes involved in the replication of the virus. Thus far, we have completed the first phase of the research and have developed multiple lead series with potent target activity, as well as activity against the virus in whole cell antiviral assays. ❖

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