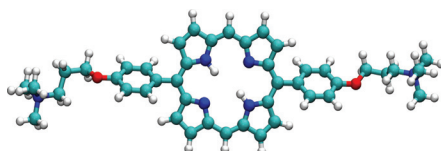


Advertisement feature

Up the Ante with Antimicrobial Agents



XF-73 from Destiny Pharma

Antimicrobial agents kill or slow the growth of bacteria, an important element in the control of deadly infectious diseases. The most commonly known group of antimicrobial agents are antibiotics, naturally produced substances from certain groups of microorganisms. However, with the increase in resistance to more and more antimicrobial agents, the role of the 'classical antibiotic' is increasingly redundant. Over the past 30 years, focus has shifted onto research into peptide antibiotics and more recently drug platforms based on novel di-cationic porphyrin molecular structures.

The development of peptides as antimicrobial agents has been historically difficult due to their association with high research and development expenses and difficult scalability. Even though peptides have shown promise as antimicrobials without the resistance problems of antibiotics, until recently the understanding of peptides has not matured enough for researchers to be able to develop synthetic analogs of natural peptides with the right pharmacological properties. However recent advancements in manufacturing processes are now helping biotech and pharmaceutical companies and research organizations to pioneer peptides which are more potent, show higher specificity and have fewer toxicology problems than antibiotics. Due to this, the potential of therapeutic peptides has recently intensified addressing hitherto unmet medical needs.

Peptide Manufacturing Technology

Biotage has launched its new **Syro Wave**, a microwave and parallel peptide synthesizer which combines the performance of its established MultiSyn Tech robotic synthesizer with microwave technology. The Syro Wave peptide synthesis system offers both microwave and parallel peptide synthesis capabilities increasing productivity, yield and purity while cutting costs and saving time. To date peptide synthesis labs have been required to invest in both standalone parallel systems for productivity and cost efficiency and standalone microwave systems for difficult or longer peptides. This results in increased demand on bench space, duplication of computer control systems and multiple operating software platforms for chemists to learn and maintain. This new technology addresses a number of these shortcomings.

New Peptides

As a result of the advance in manufacturing techniques many companies are now able to develop peptides as potential antimicrobial agents.

Novozymes has discovered an antimicrobial peptide called **Plectasin**, which is able to fight bacterial infections that have developed resistance to conventional antibiotics and acts on bacteria responsible for diseases such as pneumonia as well as *Staphylococcus* bacteria which are resistant to all existing antibiotics.

Novozymes has also found a peptide which works on Gram-negative bacteria, whereas **Plectasin** works on Gram-positive bacteria. Gram-negative bacteria are even more difficult to fight with traditional antibiotics. **Novozymes** has entered into a collaboration agreement with **Sanofi-Aventis** for further development of **Plectasin** variants. The new Gram-negative peptide discovered by **Novozymes** is still in the discovery phase along with other peptide candidates.

Pacgen Biopharmaceuticals Corporation has entered into collaboration research with **New Summit Biopharma Co.** to develop **PAC-113** for treatment of oral candidiasis for commercialisation in China. **PAC-113**, is a peptide-based anti-fungal targeting oral *Candida* infection in immunocompromised patients. It is a 12 amino-acid antimicrobial peptide derived from a naturally occurring histatin protein found in human saliva. This peptide alters the permeability of fungal cell membranes causing cell death. In addition, **PAC-113** also interacts with fungal mitochondria causing production of reactive oxygen species that lead to fungal cell destruction. The drug has passed Phase 2b clinical trials, confirming that **PAC-113** is safe and well-tolerated in patients.

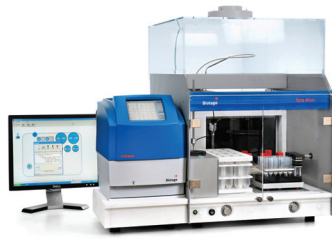
AnaSpec has announced the release of two structurally complex peptides, **Agr D1 Thiolactone** and **Agr D2 Thiolactone**, as part of its **GO™** catalog peptide offerings. In

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The Scott Partnership

T H E
SCOTT
P A R T N E R S H I P

nature@scottpr.com

www.scottpr.com



The Syro Wave from Biotage is a microwave and parallel peptide synthesizer

Gram-positive bacteria, such as in *Staphylococcus aureus* (*S. aureus*), physiological changes in the bacterial population are dependent on specific cell densities and growth phases (known as quorum sensing). *S. aureus* specifically uses quorum sensing to control the expression of exoproteins implicated in virulence through the Agr (accessory gene regulator) locus. The Agr system is activated by an accumulation of extracellular mature peptide signals known as autoinducing peptides (AIPs). *S. aureus* has four distinct Agr groups, which exhibit bacterial interference. Each Agr group synthesizes a discrete AIP sequence. All four AIP sequences are composed of seven to nine amino acids and have a thiolactone ring in the C-terminal five residues through a cysteine side chain.

Issar Pharmaceuticals has discovered an antimicrobial peptide called **Genopep** which has demonstrated sufficient control of target bacteria for the treatment of sepsis in burn patients. Sepsis accounts for greater than 50 percent of deaths related to patients who suffer from burns. The current treatment of the burned patient involves fluid resuscitation, hemodynamic stabilization and the application of topical antimicrobials prior to wound excision and grafting. Bacteria flourish in dead tissue and intravenous antibiotics cannot penetrate the tissue because of its impaired blood supply. Results of several clinical trials adopting Genopep found that the rate of wound healing was greater and scar formation was significantly lower compared to that in standard treatment groups.

Developing Drug Platforms

The challenge of bacterial resistance to antibiotics has led to the development of a range of peptide-based antibiotic and non-antibiotic novel drug platforms. Biotech and pharmaceutical companies can now develop drug platforms providing practical solutions to diseases such as MRSA, cancer and various other serious bacterial infections.

In the US **Cubist** has launched **CUBICIN**[®] (daptomycin for injection), the first antibiot-



Novozymes has discovered an antimicrobial peptide called Plectasin

ic in a new class of anti-infectives called lipopeptides. In July 2008, Cubist also began promoting **MERREM**[®] I.V. (meropenem for injection) in the US under an agreement with AstraZeneca. The Cubist clinical product pipeline currently consists of a Phase 2 program, added with Cubist's acquisition of Calixa Therapeutics Inc. in December 2009, focused on the development of a novel cephalosporin to address certain serious infections caused by multi-drug resistant (MDR) Gram-negative organisms; a program for the treatment of CDAD (Clostridium difficile-associated diarrhea), now entering Phase 2; and a Phase 1 program intended to address the unmet medical need for a treatment for serious infections caused by MDR Gram-negative pathogens. Cubist is also working on several pre-clinical programs, which would address areas of significant medical needs. These include an anti-infective program for the treatment of respiratory syncytial virus (RSV) in children, therapies to treat various serious bacterial infections and agents to treat acute pain.

Affymax has announced completion of treatment and follow-up of patients with anemia due to chronic renal failure enrolled in the four-trial, Phase 3 clinical program for the investigational drug **Hematide**. The Hematide Phase 3 program consisted of four open-label, randomized active-controlled clinical trials in the US and Europe, including two trials in dialysis patients and two others in patients not on dialysis. The PEARL 1 and PEARL 2 trials conducted in non-dialysis patients were designed to evaluate the safety and efficacy of Hematide compared with darbepoetin alfa for treating anemia and maintaining hemoglobin levels over time, based on the trial protocol. Hematide is a novel synthetic, PEGylated peptidic compound that binds to and activates the erythropoietin receptor and thus acts as an erythropoiesis stimulating agent (ESA).

Optimer Pharmaceuticals, Inc., a biopharmaceutical company focused on discovering, developing and commercializing innovative anti-infectives to treat serious infections and



Burns before and after treatment: Standard Treatment and Genopep Treatment from Issar Pharmaceuticals

address unmet medical needs, has two late-stage anti-infective product candidates, **Fidaxomicin** and Prulifloxacin. Fidaxomicin is a narrow spectrum antibiotic being developed for the treatment of Clostridium difficile infection. Optmer has reported positive top-line results from two Phase 3 trials of fidaxomicin. **Pruve**[™] is a prodrug in the fluoroquinolone class of antibiotics being developed as a treatment for infectious diarrhea. Optimer has also successfully completed two Phase 3 trials with Pruve. Optimer has also licensed technologies and therapeutic targets from The Scripps Research Institute and The Memorial Sloan-Kettering Cancer Center.

Di-Cationic Porphyrin Drug Platform

Destiny Pharma has produced a breakthrough anti-microbial drug platform (based on a novel di-cationic porphyrin molecular structure) which is being developed for the prevention/treatment of multi-drug resistant (MDR) bacterial infections such as MRSA (methicillin resistant *Staphylococcus aureus*). The novel drug action targets the bacterial cell membrane and means that bacteria can be killed while seemingly avoiding the emergence bacterial resistance. The lead drug (**XF-73**) is undergoing clinical development in the UK. The first use for XF-73 is for nasal decolonisation of MRSA from patients entering hospital. Destiny Pharma is also developing therapeutic uses of XF-73 for the treatment of established MDR bacterial skin infections.

Companies mentioned in this Product Focus:

Affymax - www.affymax.com
 AnaSpec - www.anaspec.com
 Biotage - www.biotage.com
 Cubist - www.cubist.com
 Destiny Pharma - www.destinypharma.com
 Issar Pharmaceuticals - www.issarpharma.com
 Novozymes - www.novozymes.com
 Optimer - www.optimerpharma.com
 Pacgen Biopharmaceuticals Corporation - www.pacgenbiopharm.com

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