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TARGANTA THERAPEUTICS ANNOUNCES DISCOVERY OF NEW CLASS OF AGENTS TO TARGET *STAPHYLOCOCCUS AUREUS*

- Results Represent Platform for Development of Targeted Therapies to Combat Increasing Antibiotic Resistance -

Washington, DC, December 19, 2005 - Targanta Therapeutics Inc., a private biopharmaceutical company developing innovative antibacterial drugs, presented three posters at the 45th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) which demonstrate the potential of the company's approach to combating bacterial infections.

- *Bacteriophage Proteins G1ORF240 and TwORF168 Validate the DNA Sliding Clamp of Staphylococcus aureus for Inhibitor Screening*. Adam Belley. Antibacterial Targets and Screens. Poster F-1839.

  Researchers determined that the expression of two viral proteins in *S. aureus* inhibits DNA production and therefore causes the bacteria to be destroyed. Both proteins, TwortORF168 and another phage protein, G1ORF240, bind to the DNA sliding clamp of *S. aureus* and inhibit the bacteria's ability to grow. Importantly, the investigators were able to develop a test for the *S. aureus* replicase, an enzyme that promotes DNA production, to screen for small-molecule inhibitors of DNA replication and were able to identify two inhibitors with antibacterial properties against *S. aureus* that may be developed into drugs to help fight these difficult infections. This approach may help treat patients with bacterial infection.

- *The Primary Sigma Factor of Staphylococcus aureus: from Target Identification to Isolation of Inhibitors of the RNA Polymerase Holoenzyme*. Mohammed Dehbi. Antibacterial Targets and Screens. Poster F-1845.

Researchers have identified that the antibacterial peptide G1ORF240 from a virus that binds to the primary sigma factor (a subunit of RNA polymerase that facilitates the initiation of transcription by recognizing specific DNA promoter sites) of *S. aureus*. This protein is responsible for rapidly inhibiting bacterial metabolism during phage infection and preventing further cell growth.

In order to determine which classes of compounds from chemical libraries expressed antibacterial activity against *S. aureus*, investigators first developed a primary sigma factor-dependent transcription test to screen for inhibitors and identified several small molecule inhibitors of *S. aureus* RNA polymerase (an enzyme that catalyzes the formation of DNA from precursor substances in the presence of preexisting RNA acting as a template). Based on the results of the test, researchers decided to concentrate on a class of drugs called 2-ureidothiophene-3-carboxylate ester, which selectively inhibit *S. aureus* transcription *in vitro* and display antibacterial activity against the bacteria.

- *A New Class of Small Molecule RNA Polymerase Inhibitors with Activity Against Staphylococcus aureus.* A. Rafai Far. New Antibacterial Agents Against Defined Targets Session. Poster F-1874.

  Researchers have identified a new class of selective RNA polymerase (RNAP) compounds that exhibit antibacterial properties against *S. aureus*. This discovery represents a new class of small molecule compounds that acts via the *S. aureus* RNAP holoenzyme. Investigators identified a key member of this class, 2-ureidothiophene-3-carboxylate ester, that has been shown to selectively inhibit transcription. Additionally, they were able to demonstrate the effectiveness of the compound in a mouse model of S*.aureus* infection when administered parenterally. Researchers concluded that this class of compounds may present a viable option for the treatment of *S. aureus.* More research is needed to further their development into useful therapies that will overcome the issue of resistance.

"These results demonstrate that we are charting a promising new course in the discovery of innovative platforms to help fight deadly infections," said Pierre Etienne, M.D., President and CEO of Targanta Therapeutics. "We are encouraged and excited to build upon these results and move toward clinical applications of these novel molecules."

The Growing Problem of Antibiotics

Mutating bacteria have become resistant to many existing antibiotics, making infections increasingly difficult to treat and creating a serious public health challenge. *Staphylococcus aureus* (staph), a bacterium that can lead to infections in the heart, bones, lungs and bloodstream, often proves fatal. According to the Centers for Disease Control and Prevention, over the last 30 years the percentage of staph bacteria resistant to traditional antibiotics rose by more than 50 percent in U.S. hospitals. New antibiotics to treat drug-resistant bacterial strains could significantly increase the survival rate among patients with bacterial infections.

Phage-inspired Drug Discovery Platform

By unraveling the genetic code of phages, or viruses that attack bacteria, Targanta researchers have identified antimicrobial proteins used by the phages to kill or stop the replication of the bacteria, as well as the specific bacterial targets with which those proteins interact. These targets are then used to screen hundreds of thousands of synthetic compounds to identify novel small molecule drugs that mimic the phage proteins' antimicrobial effects. Targanta's discovery efforts are currently focused on three medically and economically important human pathogens: *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*.

About Targanta Therapeutics

Targanta Therapeutics is a privately-held biopharmaceutical company developing and commercializing antibacterial drugs to treat serious infections in the hospital setting. Its pipeline includes an array of antibacterial agents in various stages of development. The company is headquartered in Indianapolis, IN, and will maintain its research and development operations in St. Laurent, Quebec. For further information about Targanta, visit the company website, www.targanta.com.

Disclaimer

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