

MICROBIOTIX, INC. RECEIVES SBIR PHASE II GRANT TO CONTINUE DEVELOPMENT OF TYPE III SECRETION INHIBITORS

August 1, 2011. Microbiotix, Inc, a privately held biotechnology company, announced that it was awarded a Phase II Small Business Innovation Research (SBIR) grant from the National Institutes of Health/NIAID. The SBIR Phase II grant entitled, "Type III Secretion Inhibitors for Anti-Infective Therapy" provides three years of support to develop pre-clinical candidates.

The increasing prevalence of antibiotic-resistant strains of bacterial pathogens represents an unmet medical need. Type-three secretion is a mechanism used by many pathogenic bacteria to increase their virulence in human infections. Bacterial toxins secreted by this method reduce the protective effect of the infected individual's own innate immune system. Successful development of an inhibitor targeting this virulence mechanism will provide a new weapon to combat acute infections such as pneumonia and bacteremia.

Pseudomonas aeruginosa infection is the leading cause of hospital-acquired pneumonia in patients undergoing mechanical ventilation. Current antibiotic treatments exhibit failure rates as high as 18%, even when the organism is susceptible to the antibiotic being administered. The goal of this project is to address this critical medical need by identifying specific inhibitors of the type III secretion system (T3SS) and developing them into novel therapeutic agents against *P. aeruginosa*. T3SS is the major virulence factor contributing to the establishment and dissemination of *P. aeruginosa* infections and is utilized by the bacterium to secrete and translocate toxin effectors into host phagocytes, thereby weakening the host's innate immune response. The presence of a functional T3SS is significantly associated with poor clinical outcomes and death in patients and markedly reduces survival in animal infection models. The T3SS inhibitors developed in this project will be administered therapeutically and prophylactically in combination with anti-pseudomonal agents to inhibit the T3SS-mediated intoxication of phagocytes and thereby potentiate a robust host innate immune response and enhance the activity of co-administered antibiotics. In Phase I, we discovered 15 novel inhibitors of *P. aeruginosa* T3SS in 3 different chemotypes, with the following properties propitious for further development: (a) novel, chemically tractable structures, (b) highest potency of any reported *P. aeruginosa* T3SS inhibitors ($IC_{50}=1 \mu M$), (c) selectivity indices (CC_{50}/IC_{50}) >100 , (d) favorable preliminary structure-activity relationships (SAR), including strict stereo-specificity of activity, clear definition of substituent size at the stereocenter, and identification of five modifications in three regions of the scaffold that increase potency; and (e) not subject to efflux in *P. aeruginosa*. Our strategy in Phase II is to optimize the most promising of these structures as preclinical candidates. Biochemical and molecular genetic approaches will be applied to identify the molecular target of these inhibitors and the frequency of mutation to resistance. Following toxicity and pharmacokinetic assessment, inhibitors will be tested for efficacy as single agents and in combination with anti-pseudomonal agent ceftazidime in two murine models of *P. aeruginosa* infection, acute pneumonia and bacteremia. The major milestone of this proposal is to select anti-T3SS pre-clinical candidates, which will be advanced to Investigational New Drug (IND) enabling toxicology and safety pharmacology studies in Phase III of this project.

We will accomplish the following specific aims: (1) synthesize structurally diverse analogs of the phenoxyacetamide hit series based on structure-activity relationships; (2) prioritize analogs by potency and selectivity of T3SS inhibitory activity, as well as favorable ADME properties; (3) identify the molecular target of the phenoxyacetamide T3SS inhibitor series and the frequency of resistance; (4) determine acute toxicity, pharmacokinetic parameters, and efficacy of lead compounds in animal models.

Donald Moir, Ph.D., Chief Scientific Officer, will serve as the Principal Investigator of the grant.

About Microbiotix

Founded in 1998, Microbiotix, Inc. is a product-focused biopharmaceutical company engaged in the research and development of novel, small-molecule, anti-infective drugs that address commercially significant medical markets. The company currently has several active research programs in the fields of anti-bacterial and anti-viral discovery, with three compound series in pre-clinical development. More information can be found on the company's web site, www.microbiotix.com.