Sequella Licensing Opportunity
SQ609 Therapeutic: Pre-clinical
Indication: Treatment of Pulmonary TB

Sequella Incorporated

SQ609
A Small Molecule Antibiotic

SQ609 is an orally active antibiotic for treatment of pulmonary tuberculosis (TB). Currently entering IND-directed preclinical safety, pharmacology, and toxicology studies, SQ609 could be used to increase efficacy of first-line TB drug regimen, simplify therapy, and/or shorten the TB treatment regimen for drug sensitive and drug resistant TB.

Overview

Over the last 10 years, Sequella drug R&D focused on discovery of new scaffolds with antimycobacterial activity and development of new drugs for the treatment of TB. As a result of these studies, we identified novel classes of antitubercular compounds that are structurally distinct and different in mechanism of action from existing TB drugs. One intriguing class was a series of compounds derived from a 25,000-compound library based on changing the ethylene bridge of 1,2 ethylenediamines. Many of these compounds contained a dipiperidine pharmacophore. Several compounds in the dipiperidine class demonstrated good activity against *M. tuberculosis* (Mtb), low nonspecific cytotoxicity, a selectivity index indicative of a suitable therapeutic window, and good logP values (*in silico* predictor of intestinal absorption). The dipiperidine hits included adamantane-containing hydroxydipiperidine, SQ609, and further studies demonstrated SQ609 to be the most promising compound of its class. A summary of its attributes includes:

- Potent *in vitro* activity against laboratory and clinical strains of Mtb
- Inhibition of Mtb by interfering with cell wall biosynthesis
- Moderate *in vitro* cytotoxicity in cultured mammalian cells
- Suitable therapeutic window (*in vitro*)
- Active against intracellular Mtb
- Active against single-drug resistant strains of Mtb (Isoniazid, Rifampin, and Streptomycin),
- High specificity for Mtb
- Good aqueous solubility
- Orally activity by itself in two different mouse models of TB
- Able to prolong therapeutic effect after withdrawal of single and multiple drugs during therapy in mice
- Activity better than TB standard of care (1-2 $\log_{10}$) when administered in combination with isoniazid, rifampin, and pyrazinamide in murine models of TB
- Favorable *in vitro* safety pharmacology and ADME profile

Alliance and Market Opportunities

Sequella is seeking partners for development and commercialization of SQ609. Based on several independent studies, the drug's worldwide market potential is approximately $400 million, with the majority of sales expected in the Established Market Economies (EME).

Market Need. In the U.S., there are an estimated 15 to 30 million people suspected to have TB infection; annually there are roughly 15,000 reported new cases of active disease. Worldwide there are an estimated 2 billion persons infected with *M. tuberculosis* and nearly 10 million active cases of TB. The total high-risk population for TB in the U.S. casts a wide net and includes the following segments:

- **Opportunistic Infection:** Persons with HIV/AIDS, immunosuppressive cancers, or illicit drug abusers
- **Healthcare:** Hospitals (both staff and patients), nursing homes, and facilities for the elderly
- **Schools and Universities:** Students and faculty in schools ranging from nursery school to colleges
- **Immigrants:** Individuals born outside the U.S. or the EU
- **Public Welfare:** Employees of prisons and jails, homeless shelter workers and residents

Approximately 450,000 patients are treated or prophylaxed for TB annually in the U.S.

Sequella Incorporated • 9610 Medical Center Drive • Suite 200 • Rockville, MD 20850
Phone: (301) 762-7776 • Fax: (301) 762-7778 • www.sequella.com

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Competitive Advantage

The current World Health Organization (WHO) recommended therapeutic regimen for TB requires administration of four drugs (Isoniazid, Rifampin, Pyrazinamide, and Ethambutol or Streptomycin) for the first two months, followed by four months treatment with Isoniazid and Rifampin. This six month regimen has had a dismal compliance rate (30-60%) based on significant side effects and the inconvenience of daily therapy.

Decades of misuse of existing antibiotics and poor compliance have created an epidemic of drug resistance that threatens TB control programs worldwide. In countries where adequate supplies of the drugs are not readily available, the prevalence of multi-drug resistant TB (MDR-TB) is as high as 50%. In the U.S., 13% of TB isolates are resistant to at least one of the first-line drugs and ~2% of isolates are resistant to more than one drug.

Since chemotherapy for MDR-TB involves less potent and more toxic 2nd line drugs, MDR-TB is harder to treat, requires longer regimens (up to 2 years), and is more dangerous (mortality range 40-80%). In early 2006, clinicians began reporting the isolation of extreme drug resistant Mtb (XDR-TB) that is resistant to the two most important front-line TB drugs, Rifampin and Isoniazid, and also resistant to at least two classes of second-line drugs. Currently, 4% of clinical isolates from MDR-TB patients in the U.S. are XDR-TB.

SQ609 has unique characteristics that give it the potential to be an important new tool in the treatment of both drug sensitive TB and MDR/XDR-TB. The TB medical and public health communities have defined the desirable characteristics of a new anti-TB drug (see table below).

Desired Characteristic	SQ609
Orally active	**Yes**
Long-acting	**Yes**
Novel mechanism of action	**Yes**
Absence of cross-resistance/antagonism with existing TB drugs	**Yes**
Synergistic or additive effects with existing TB drugs	**Yes**
Inexpensive to manufacture	**Yes**
Favorable PK/PD	**Yes**
Efficacious therapeutic window	**Yes**
Activity against drug resistant Mtb	**Yes**
Activity against non-replicating Mtb (latent)	**Yes**
Potential drug-drug interactions with HIV therapeutics (HAART Regimen)	**No**

Intellectual Property

Sequella U.S. patent application claims for SQ609 composition of matter and use have been approved as of September 2009, and Sequella has additional patent filings in the EME and select ROW countries for composition of matter and uses of SQ609 and additional dipiperidine anti-infectives. These patents provide broad coverage for chemical structure, methods, and use claims for treatment of infectious disease, anti-tubercular drugs, and proprietary dipiperidine compounds.

For information on alliance opportunities, contact:

Alan Klein, Executive Vice President, Corporate Development
Sequella, Inc. • 9610 Medical Center Drive • Suite 200 • Rockville, MD 20850
Phone: 301-762-7776 • Fax: 301-762-7778 • alanklein@sequella.com