

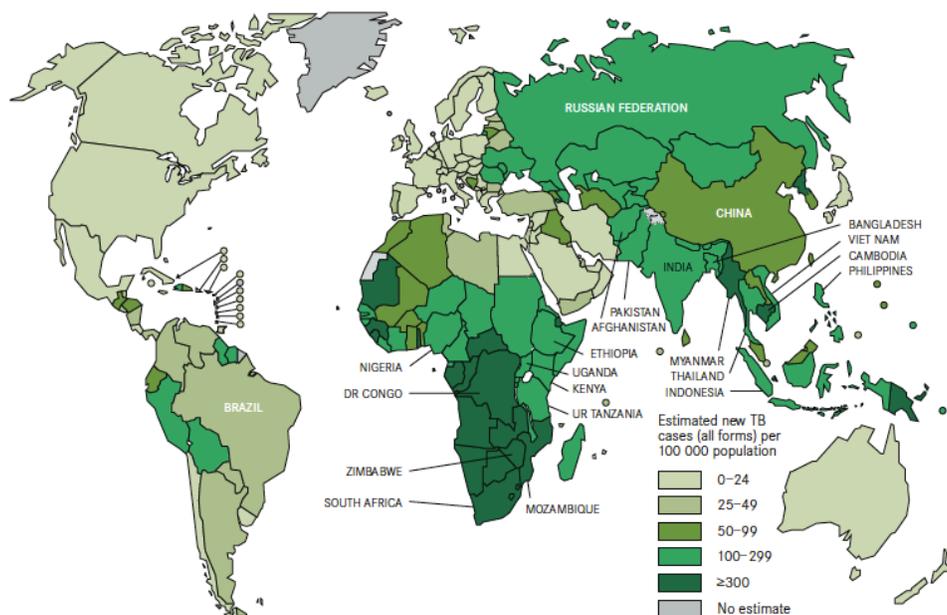
# SQ109 for the Treatment of Tuberculosis

## Clinical Development Status: Phase 2

Since 2000, Sequella has applied its scientific expertise in tuberculosis (TB) research to develop SQ109, a promising drug candidate that was discovered in partnership with the National Institutes of Health in a screen for activity against *M. tuberculosis* (Mtb). SQ109 was selected as best in class from a 63,000 compound library of diamines and underwent extensive preclinical studies in rats, dogs, and monkeys. It was safe and well-tolerated in three Phase 1 clinical trials, and a Phase 2 clinical trial was completed in late 2011.

### TB is a public health crisis and unmet medical need.

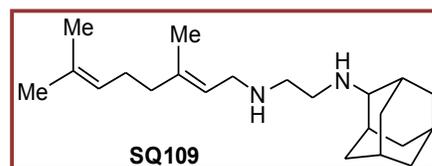
TB is the cause of the largest number of human deaths attributable to a single etiologic agent, killing nearly 2 million people each year. The poor efficacy of existing TB drugs requires that they be administered in a multidrug regimen for at least six months. This results in poor patient compliance and leads to development of multidrug-resistant TB (MDR-TB) and extremely drug-resistant TB (XDR-TB). MDR-TB and XDR-TB are even more difficult to treat



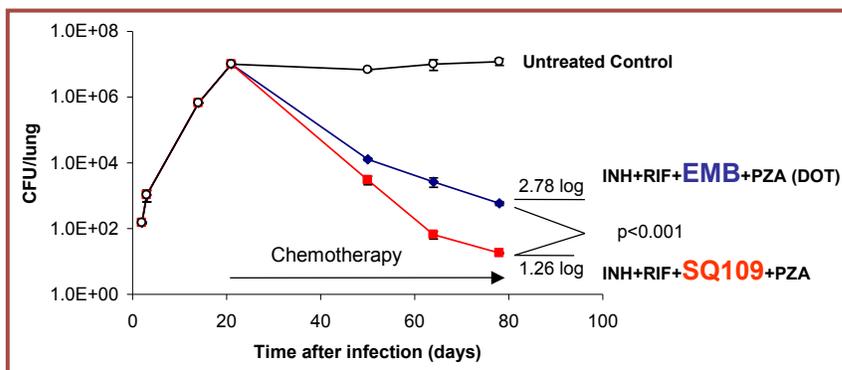
(5-8 drugs for up to 24 months) and have significantly higher mortality. Decades of misuse of existing antibiotics and poor compliance have created an epidemic of drug resistance that threatens TB control programs worldwide. New drugs and treatment regimens with activity against drug-susceptible and drug-resistant TB are desperately needed to manage this public health crisis.

### SQ109 has promising activity against drug-susceptible and drug-resistant TB.

SQ109 was discovered by screening a combinatorial library of more than 63,000 compounds with a whole-bacterium high throughput screen.<sup>1,2</sup> It is orally bioavailable with a distinctive pharmacological profile<sup>3-5</sup> and has excellent activity against all forms of Mtb, including profoundly drug-resistant clinical strains. The *in vitro* bacterial mutation rate for SQ109 is very low ( $>10^{-11}$ ), which could limit the development of drug resistance to SQ109. Finally, SQ109 has synergy with many existing TB drugs, as well as all the other promising drug candidates in clinical development.<sup>6-8</sup> This is important because TB will always be treated with more than one drug, and SQ109 synergy suggests that it may be an excellent component of a new TB drug regimen.



**SQ109 replacement of Ethambutol (EMB) in the standard TB treatment regimen leads to significantly improved efficacy.** Several *in vivo* studies in the chronic mouse model of TB using combinations of SQ109 and standard anti-TB drugs demonstrate both better efficacy and shorter time to achieve the same reduction in Mtb as standard therapy with ethambutol.<sup>9</sup>



In studies in which SQ109 replaced EMB in the standard first-line treatment regimen, no or few bacteria were cultured from lungs of mice treated for 2 months, suggesting that SQ109 results in a more rapid cure.

**Clinical Development.** SQ109 received FDA Fast Track and Orphan Drug designation in 2007. SQ109 is currently in clinical development for the treatment of adult pulmonary TB caused by drug sensitive or drug resistant strains of *M. tuberculosis* (IND #69,597, 2006). In three single and multi-dose Phase 1 clinical studies, SQ109 was both safe and well-tolerated up to 300 mg daily (highest dose tested) for up to 14 days. Enrollment in a 14-day phase 2a efficacy study designed to evaluate early bactericidal activity in TB patients in South Africa was recently completed, and no serious adverse events were observed.

**Market for New TB Drugs.** The combined U.S. and EU market only for treatment of TB and latent TB is estimated to be \$400M. In the U.S., an estimated 15-30M people are latently infected with Mtb, approximately 450,000 of whom are treated or prophylaxed for TB annually. Worldwide, 2 billion people are latently infected with *M. tuberculosis* and there are nearly nine million active cases of TB.

**Intellectual Property.** Sequella has 20 or more issued patents and additional patent filings, including U.S., E.U., Japan and China patents for compositions of matter and uses of diamine anti-infectives that cover SQ109 and derivatives. These patents provide broad coverage for composition, methods, and use claims for treatment of tuberculosis, *H. pylori* infections, systemic fungal agents, and other infectious pathogens. Sequella SQ109 patent family contains issued and pending patents in the U.S., EU, Japan, EME, South Africa, China, Eurasia, and other key international markets.

**Partnerships.** SQ109 was licensed to Maxwell Biotech Venture Fund for the treatment of TB and MDR-TB in the Russian Federation and Commonwealth of Independent States. It is available for licensing for all other areas.

**References.** Copies of all referenced papers are available upon request: please contact [katherinesacksteder@sequella.com](mailto:katherinesacksteder@sequella.com).

1. Lee RE, Protopopova M, Crooks E, Slayden RA, Terrot M, Barry CE, 3rd. Combinatorial lead optimization of [1,2]-diamines based on ethambutol as potential antituberculosis preclinical candidates. *J Comb Chem* 2003;5:172-87.
2. Protopopova M, Hanrahan C, Nikonenko B, et al. Identification of a new antitubercular drug candidate, SQ109, from a combinatorial library of 1,2-ethylenediamines. *J Antimicrob Chemother* 2005;56:968-74.
3. Jia L, Tomaszewski JE, Noker PE, Gorman GS, Glaze E, Protopopova M. Simultaneous estimation of pharmacokinetic properties in mice of three anti-tubercular ethambutol analogs obtained from combinatorial lead optimization. *J Pharm Biomed Anal* 2005;37:793-9.
4. Jia L, Noker PE, Coward L, Gorman GS, Protopopova M, Tomaszewski JE. Interspecies pharmacokinetics and in vitro metabolism of SQ109. *Br J Pharmacol* 2006;147:476-85.
5. Jia L, Coward L, Gorman GS, Noker PE, Tomaszewski JE. Pharmacoproteomic effects of isoniazid, ethambutol, and N-geranyl-N'-(2-adamantyl)ethane-1,2-diamine (SQ109) on *Mycobacterium tuberculosis* H37Rv. *J Pharmacol Exp Ther* 2005;315:905-11.
6. Chen P, Gearhart J, Protopopova M, Einck L, Nacy CA. Synergistic interactions of SQ109, a new ethylene diamine, with front-line antitubercular drugs in vitro. *J Antimicrob Chemother* 2006;58:332-7.
7. Reddy VM, Einck L, Andries K, Nacy CA. In vitro interactions between new antitubercular drug candidates SQ109 and TMC207. *Antimicrob Agents Chemother* 2010;54:2840-6.
8. Horwith G, Protopopova M, Iyer L, Mirsalis J, Sewezey R. Drug-drug interaction studies of SQ109 with first-line anti-TB drugs. In: International Workshop on Clinical Pharmacology of Tuberculosis Drugs; 2008.
9. Nikonenko BV, Protopopova M, Samala R, Einck L, Nacy CA. Drug therapy of experimental tuberculosis (TB): improved outcome by combining SQ109, a new diamine antibiotic, with existing TB drugs. *Antimicrob Agents Chemother* 2007;51:1563-5.