SQ641 for the Treatment of *Clostridium difficile* Infection

*Development Status: Preclinical*

In 2004, Sequella in-licensed from Daiichi-Sankyo a novel class of antibiotics, capuramycins, that target the essential bacterial enzyme Translocase-1. Since this enzyme is absent in human cells, it is a particularly attractive target for antibiotic development. SQ641 is a semi-synthetic compound derived from capuramycin. While SQ641 was originally identified by its excellent *in vitro* activity against the bacteria that cause TB, we discovered that it also has significant activity against *C. difficile* both *in vitro* and in a mouse model of *C. difficile* infection (CDI).

*C. difficile* infection (CDI) is an enormous problem in health care settings. *C. difficile* is the major cause of nosocomial, antibiotic-associated diarrhea, an increasingly troublesome emerging drug-resistant healthcare-associated infection. Approximately 500,000 cases of CDI occur each year in US hospitals and long-term healthcare facilities resulting in 20,000 deaths. Moreover, CDI has expanded beyond healthcare settings, and can now be community-acquired, seen in younger individuals without prior recent antibiotic use. The current standard of treatment involves antibiotics that are only transiently effective, which contributes to high relapse rates (20-30%) and further prolongs *C. difficile* shedding and transmission.

SQ641 has efficacy *in vivo* against acute CDI and prevents recurrence of disease. SQ641-treated mice developed minimal disease and did not relapse during the observation period, unlike vancomycin. This suggests that SQ641 may have benefits that exceed those of the current gold standard drug for the treatment of CDI.

SQ641 achieves and maintains high concentrations in the colon. We performed a preliminary evaluation of the pharmacokinetic properties of SQ641. Significant quantities of SQ641 remain in the colon and small intestine, achieving levels more than 100x the MIC for *C. difficile*. Even 8 hours after administration, the concentration in the colonic tissue is 10x the MIC. No SQ641 was observed in blood or liver, suggesting minimal or no systemic exposure.

In summary, SQ641 is a promising candidate for the treatment of CDI with the following characteristics:

- Inhibits a pathway essential in bacterial cell wall synthesis that has not yet been commercially exploited;
- Inhibits a known essential target that is not present in eukaryotic cells (including human cells);
- Efficacious in a mouse model of acute CDI and prevents recurrence of disease;
- Not orally bioavailable, which may be particularly suitable for efficacy against *C. difficile*; and
- Achieves concentrations >100 the MIC for *C. difficile* in the colon, the major site of colonization.

Market for New *C. difficile* Drugs. The potential U.S. market for a new drug to eradicate *C. difficile* is estimated to be $200-$300M. Each year in the U.S., there are 65,000 hospital-acquired cases, 50,000 hospital-acquired, post-discharge cases, and 263,000 nursing home-onset cases, resulting in $4 billion in excess healthcare costs.

Intellectual Property. Sequella has exclusive worldwide rights, excluding the Middle East, for all indications. Capuramycin patents include issued U.S. patent for composition of matter and uses of Capuramycin anti-infectives. These patents provide broad coverage for composition, methods, and use claims for treatment of infectious diseases by Capuramycin compounds, including SQ641.