



SUBCONTRACT EXECUTIVE SUMMARY

In Vivo Pharmacology and Toxicology¹

Research Triangle Institute, International

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Research Triangle Institute will furnish the SMA Project with pharmacological, pharmacokinetic (PK), and toxicological measurements and analyses in vivo to assist in the selection of candidate compounds to be used in efficacy screening.

The objectives of this project are to:

- 1) Assess the metabolic and blood-brain barrier permeability of a large number of candidate compounds. This screening will be performed using the following assays:
 - S9 liver fractions from human and mouse cells
 - MDCK-MDR assay of transporter mediated efflux
- 2) Determine the formulation and stability profiles of candidate lead compounds for use in all in vivo studies, and develop a method of detection in plasma, brain, and other tissues.
- 3) Establish bioavailability in brain and plasma to determine of lead compounds before initiation of efficacy screening. Such assessments will include determination of compound half-life, absorption, and distribution.
- 4) Determine the maximum tolerated dose of candidate lead compounds in neonatal mice.
- 5) Determine neurotoxicity of candidate lead compounds in adult mice.
- 6) Establish PK profiles in plasma and brain of drug-dosed model mice.

The analyses and determinations established in the above experiments will be pivotal in selecting compounds for efficacy screening. In addition, the formulation, stability, and method development results will aid in selection of dose and administration.

¹ A proposal to support this subcontract was submitted to the SMA Project's RFP JL-19704-1, "A Mouse Testing Facility for Screening of Small Molecule Therapeutics for Spinal Muscular Atrophy." SAIC provides management support for the SMA Project to the NINDS through contract N01-NS-3-2356.