



In Vivo Efficacy Testing to Support the SMA Project¹

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Key components of the behavioral and pathologic phenotypes of severe (type I), moderate (type II), and mild (type III) SMA can be recapitulated in transgenic/knock-out mice containing genetic modifications in the human and mouse survival motor neuron (SMN) gene. For example, mice homozygous for the targeted *SMN1* gene that carry the *SMN2* transgene exhibit symptoms and neuropathology similar to patients afflicted with type I SMA.^{2,3} Another type I SMA mouse, termed SMA Δ 7 mice, contain an additional *SMN1* cDNA lacking exon 7.^{4,5} Mice that are homozygous for the targeted mutant *SMN1* gene and the *SMN2* allele, and hemizygous for the *SMN1**A2G transgene, termed SMA A2G mice, exhibit symptoms and neuropathology similar to patients afflicted with type III SMA.^{6,7} Another SMA mouse model involves mice that are homozygous for the *Smn*^{tm1Hung} targeted mutation and hemizygous for the *SMN2* transgene; there is a strong correlation in these mice between estimated copy number of the transgene and severity of the phenotype.^{8,9} These mouse models can be used to evaluate potential therapeutic strategies for SMA.

PsychoGenics, Inc. will furnish the SMA Project with a core service facility with capabilities for efficacy testing of small molecule candidate compounds in mouse models of SMA. These activities are important components of the SMA Project's virtual drug discovery and development enterprise.

The three objectives of this project are to:

- 1) Establish, maintain, and characterize a self-sustaining breeding colony of type-1 SMA Δ 7 mice of sufficient size for phenotyping and compound testing.
- 2) Establish a self-sustaining breeding colony of SMA A2G mice and characterize early outcomes measures in these mice.
- 3) Perform efficacy testing in SMA Δ 7 mice.

PsychoGenics will also develop reliable phenotyping assays for assessing therapeutic efficacy in type-1 SMA Δ 7 and SMA A2G mice. PsychoGenics, Inc. may also establish, maintain, and characterize SMA mouse models other than those listed above, conduct efficacy testing in additional SMA model mice (e.g., A2G mice), and perform additional tasks as requested.

¹ A proposal to support this subcontract was submitted to the SMA Project's 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.

² Monani, U.R., Sendtner, M., Coovert, D.D., Parsons, D.W., Andreassi, C., Le, T.T., Jablonka, S., Schrank, B., Rossol, W., Prior, T.W., Morris, G.E., Burghes, A.H.M. 2000. The human centromeric survival motor neuron gene (SMN2) rescues embryonic lethality in *Smn*(^{-/-}) mice and results in a mouse with SMA. *Human Molecular Genetics* 9(3): 333-9.

³ <http://jaxmice.jax.org/jaxmice-cgi/jaxmicedb.cgi?objtype=pricedetail&stock=005024>.

⁴ Le TT, Pham LT, Butchbach ME, Zhang HL, Monani UR, Coovert DD, Gavrilina TO, Xing L, Bassell GJ, Burghes AH. 2005. SMNDelta7, the major product of the centromeric survival motor neuron (SMN2) gene, extends survival in mice with spinal muscular atrophy and associates with full-length SMN. *Human Molecular Genetics* 14(6):845-57.

⁵ <http://jaxmice.jax.org/jaxmice-cgi/jaxmicedb.cgi?objtype=pricedetail&stock=005025>.

⁶ Monani, U.R., Pastore, M.T., Gavrilina, T.O., Jablonka, S., Le, T.T., Andreassi, C., DiCocco, J.M., Lorson, C., Androphy, E.J., Sendtner, Podell, M., Burghes, A.H.M. 2003. A transgene carrying an A2G missense mutation in the SMN gene modulates phenotypic severity in mice with severe (type 1) spinal muscular atrophy. *J. Cell Biology*, 160(1):41-52.

⁷ <http://jaxmice.jax.org/jaxmice-cgi/jaxmicedb.cgi?objtype=pricedetail&stock=005026>.

⁸ Hsieh-Li, H.M., Chang, J., Jong, Y., Wu, M., Wang, N., Tsai, C.H., Li, H. 2000. A mouse model for SMA. *Nature Genetics*, 24:66-703.

⁹ <http://jaxmice.jax.org/jaxmice-cgi/jaxmicedb.cgi?objtype=pricedetail&stock=005058>.