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TITLE: Therapeutic Value or Harm of Neuregulin 1 in Demyelinating Disorders

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14. ABSTRACT It is still not clear whether the primary process in multiple sclerosis is degenerative, immunological, or both. In fact, both demyelination/remyelination of axons and micogolial immune activation are important observations both in patients with MS and in animal models. Neuregulin 1 is both a membrane bound and secreted growth and differentiation factor that regulates glial development and survival, synaptogenesis, axoglia interactions, and recently microglial activation. Given these diverse actions, NRG1 could be a potential therapeutic target for CNS demyelinating disorders. However, it is unclear whether NRG1 would actually be helpful or harmful as a therapeutic treatment because of its diverse effects. In this proposal we will test a novel, targeted fusion protein that specifically disrupts neuregulin1 signaling in an inducible transgenic mouse model to determine the effects of NRG1 signaling in two demyelinating animal models. The therapeutic efficacy of this entirely humanized antagonist is achieved by combining NRG1's own heparinbinding domain with a NRG1 receptor decoy so tha tit targets the same that NRG1 does. Transgene induction at different stages of both the cuprizone and EAE models will be used to determine both the effects of NRG1 on disease progression as well as on demyelination and remyelination on tissues. Whether or not NRG1 signaling is beneficial or harmful in these models, the availability of both NRG1 agonists and antagonists could rapidly lead to biologically driven, targeted therapeutics in patients with multiple sclerosis and other demyelinating disorders.					
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INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

BODY:

As we indicated in the SOW, we need HBD-S-H4/GFAP double Tg mice and C57BL/6 wild type control mice for Tasks 1 and 2. This is why we have asked for a no cost extension as listed below together with our progress to date:

- 1) We found that Jackson C57BL/6 mice have been very low incidence for inducing EAE since September 2011. Regarding to solving the problems, we have contacted to Jackson but they has not known what are causing the problems. We also have asked a number of life time experienced EAE colleagues, they told us about these kind of Jackson mice problems used to last more than 6 months, and then the mice problems would go away.
- 2) Our HBD-S-H4/GFAP colony did not breed well at the beginning when the grant started. In 2012, we dramatically increased our breeding cases and we are getting a lot of pups currently. However, we just have been informed by the WSU animal facility: our animal room is infected by rotavirus on May 10, 2012. Therefore, we have to stop breeding the colony since the virus lives in the body of young pups. Also we can't perform any disease models in the adult animal because the virus affects adult's immune system. Since the treatment to the virus will take 6 weeks, w have to wait to breed mice again until the room becomes to rotavirus negative.
- 3) Based on the mice problems above, we will need one year no cost extension to finish the SOW.

KEY RESEARCH ACCOMPLISHMENTS:

Despite this delay, we have some preliminary results to suggest that mice with EAE that express HBD-S-B4 have less severe disease, but the number of animals does not reach significance.

REPORTABLE OUTCOMES: None as of yet

CONCLUSION:

Given the long time it takes to breed these mice into the proper genetic background, it has taken longer than expected. However, if we continue to see less disease severity in mice that express the Neuregulin antagonist, the 'so what' is that we will potentially have a new therapeutic to treat MS.

REFERENCES: Other related publications from the laboratory, but not directly supported by this grant:

Ma Z, Wang J, Song F, Loeb JA (2011) Critical Period of Axoglial Signaling between Neuregulin-1 and Brain-Derived Neurotrophic Factor Required for Early Schwann Cell Survival and Differentiation, J Neurosci. 31(26):9630-40.

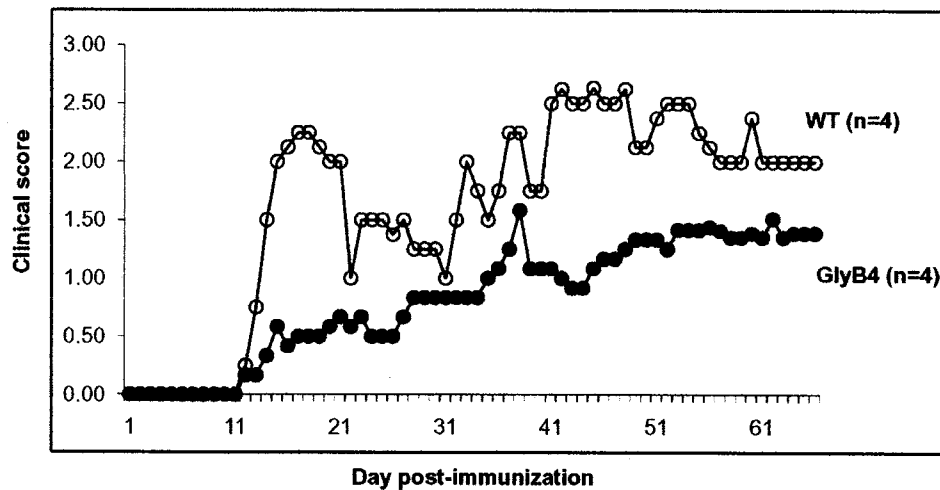
Song F, Chiang P, Wang J, Ma Z, Ravits, J, Loeb JA. (2012) Abberant neuregulin 1 signaling in amyotrophic lateral sclerosis. J Neuropath Exp Neurol, 71:104-15.

APPENDICES: none

SUPPORTING DATA:

Here is some new preliminary findings on the effects of HBD-S-H4 on EAE severity when the EAE was working better in the C57/B6 strain from Jackson labs.

Decreased EAE (MOG) disease severity in GlyB4 Transgenic mice



Mice	Incidence of EAE (%)	Mean Day of Onset	Mean cumulative Clinical Score	Mean Maximum Severity	Mortality (dpi 41)
WT (2M+2F)	4/4 (100%)	12.25 ± 1.26	106.14 ± 14.86	3.63 ± 0.84	0/4 (0%)
GlyB4 Tg (3M+3M)	6/6 (100%)	20.17 ± 9.91	<u>45.98 ± 25.68**</u>	<u>2.25 ± 0.99*</u>	0/6 (0%)

P=0.003

P=0.03