

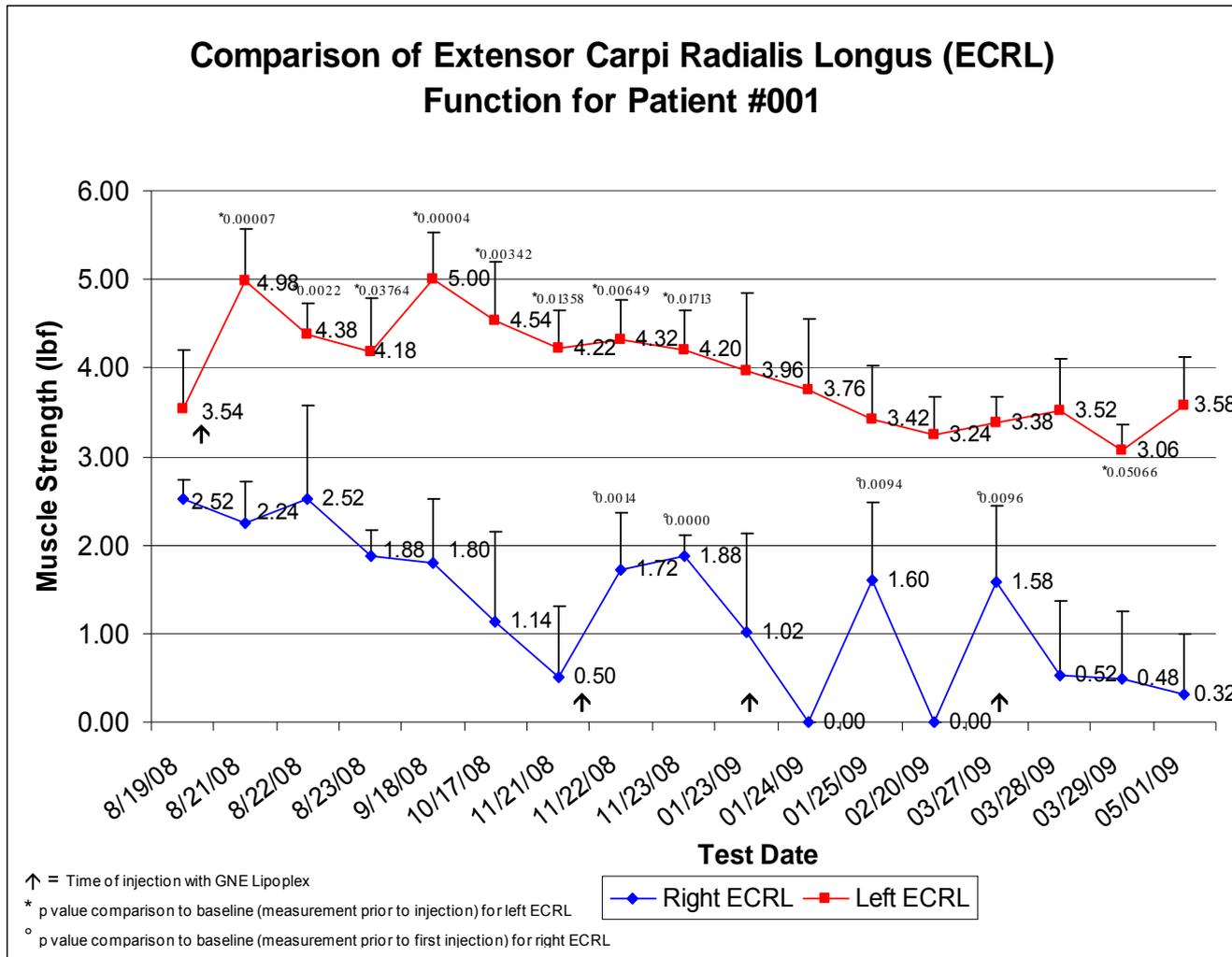
A Phase I Compassionate Trial of Nanocomplex Mediated GNE Gene Replacement in Hereditary Inclusion Body Myopathy-2

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Recombinant DNA Advisory Committee
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Results after Intramuscular Administration in Single Patient

- No significant toxic effect observed
- Transient muscle function improvement in BOTH left and right ECRL

Results after Intramuscular Administration in Single Patient

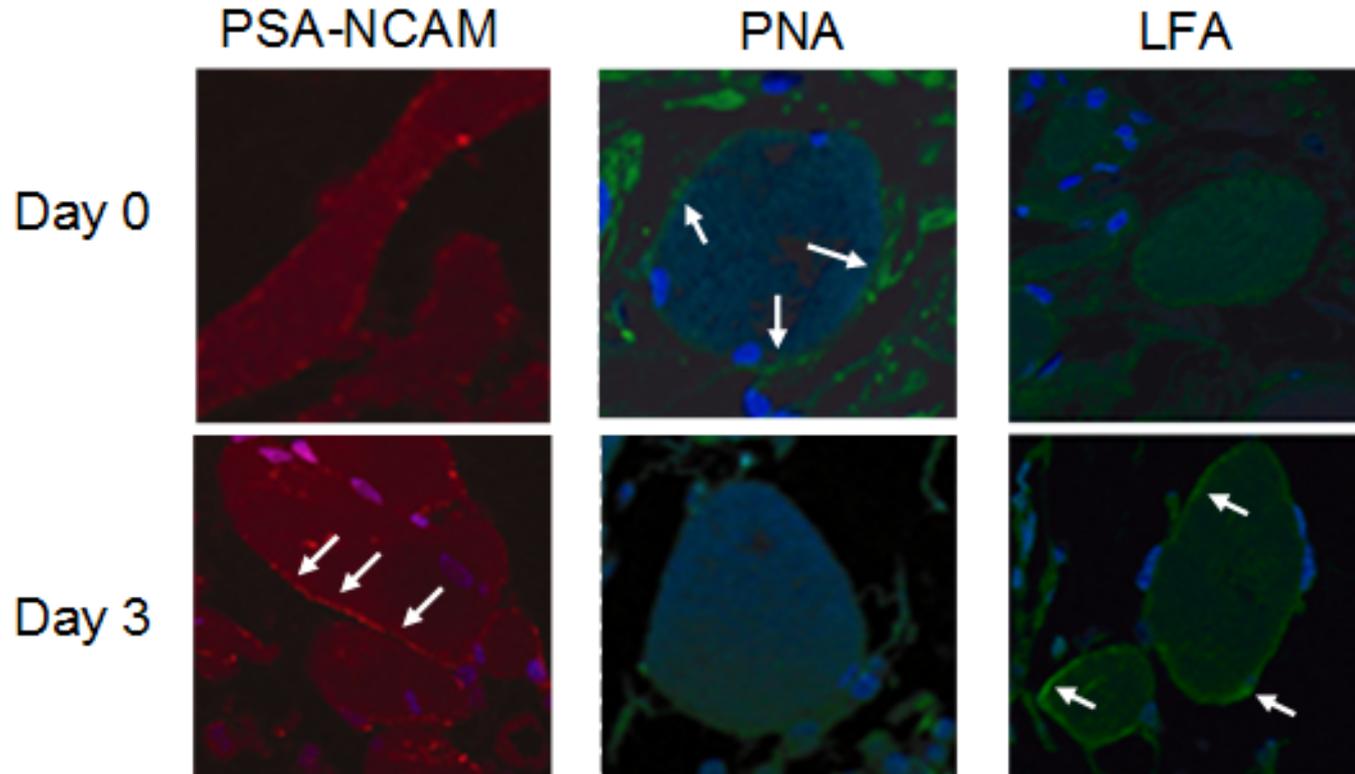


Results after Intramuscular Administration in Single Patient

- Left arm treatment with GNE-Lipoplex mediated a significant effect lasting up to 150 days
- This correlated with transient GNE transgene expression and prolonged detection and increase in sialic aci.

Time Point	GNE mRNA in muscle (fg)		Sialic Acid in Muscle (nmol NANA / mg protein)	
	Average	StDev	Average	StDev
Day 0	0	0	22.2	2.1
Day 3	1957	3783	27.7	0.4
Day 30	0	0	27.6	2.7

Antibody Staining of Sialic Acid Dependent Proteins L-ERCL Muscle Biopsy Pre/Post GNE Lipoplex Injection

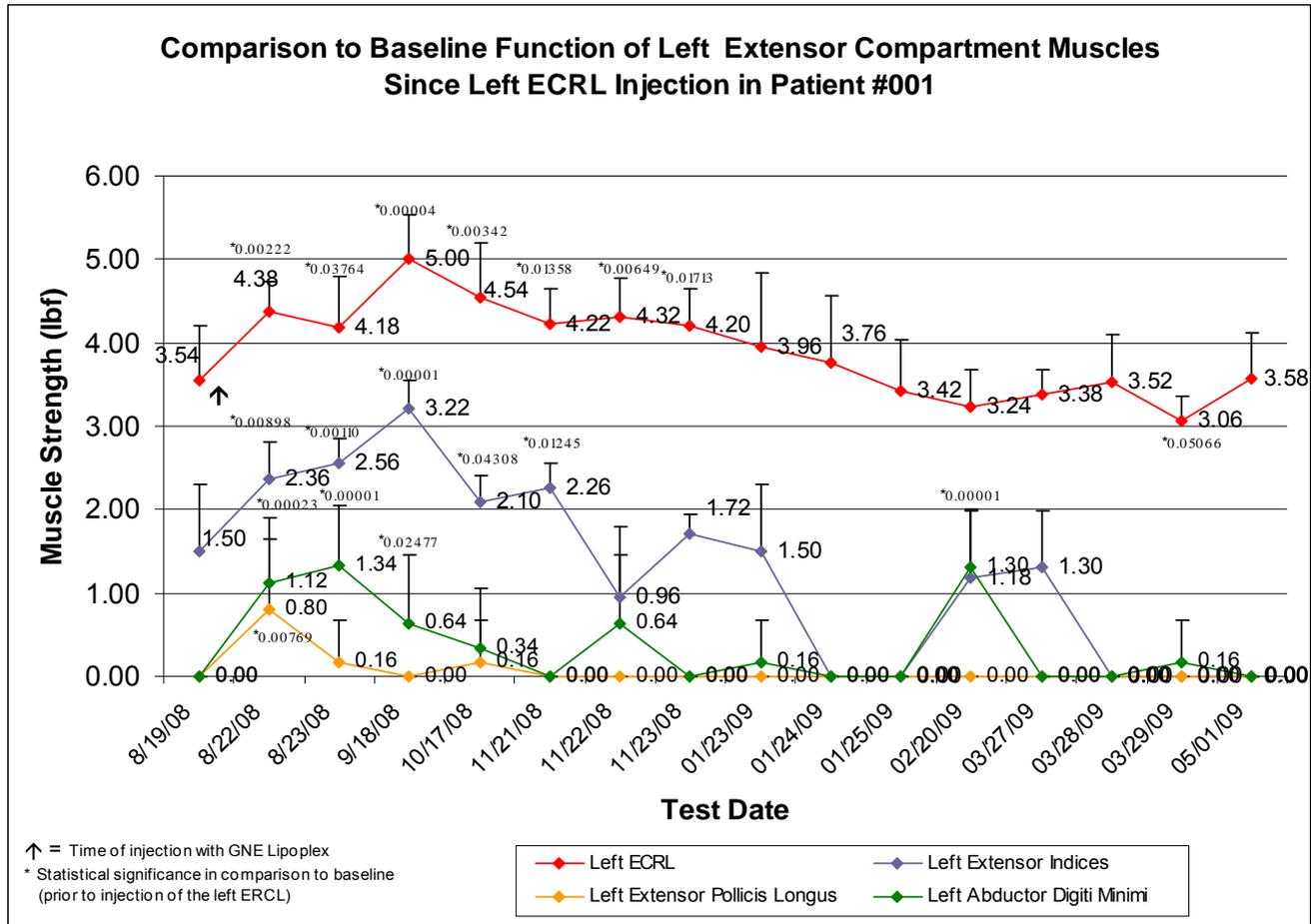


PSA-NCAM is hyposialylated in HIBM muscle. PNA stains O-linked glycans if terminal sialic acid is missing. LFA stains bound sialic acid and CMP-sialic acid. Arrows indicate positive staining for each treatment. The combined staining results indicate an increase in sialic acid production at Day 3.

Summary

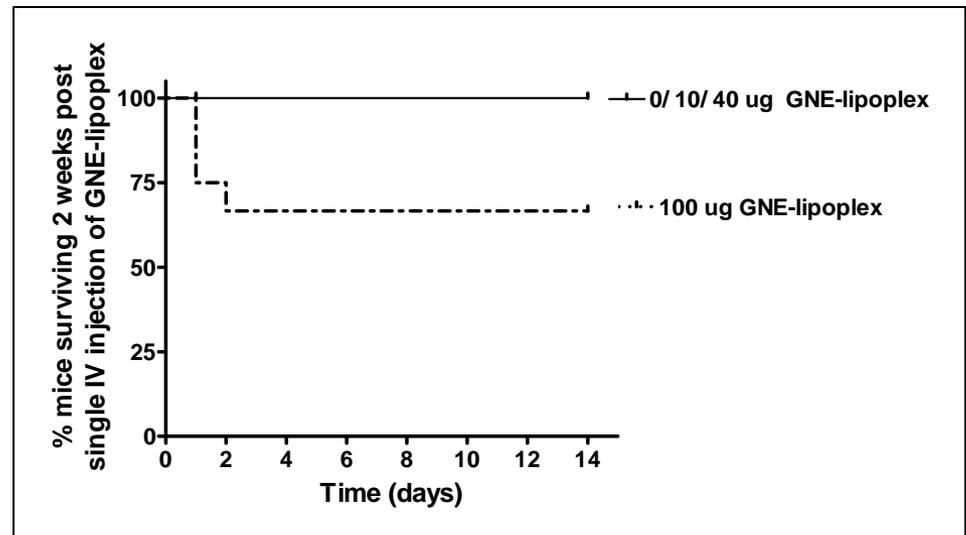
- No significant toxic effect to IM dosing at 0.4 mg/inj (except Grade 1 fever) observed
- Sialic acid increase correlated with injected muscle function increase
- Transient increase in muscle function was observed in regional muscles adjacent to left ECRL

Transient increases in Muscle Function in regional muscles Adjacent to the Left ECRL



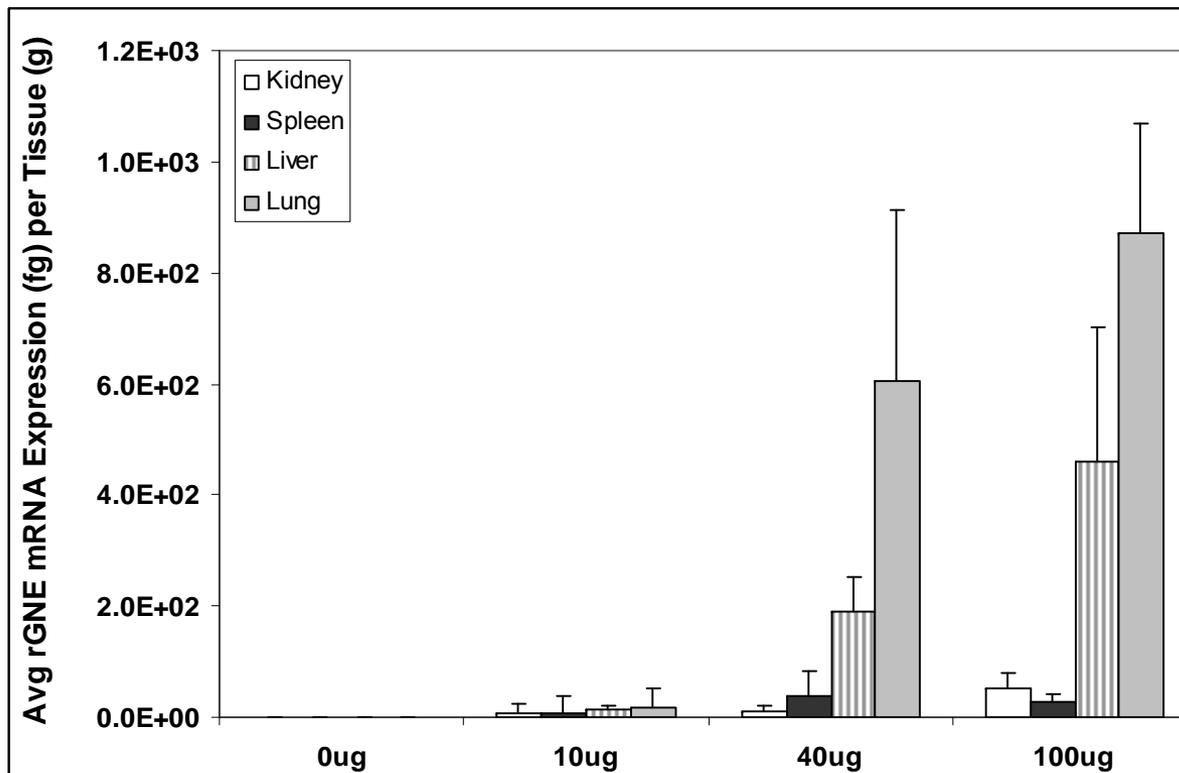
Animal IV Trial Results

- No deaths were observed at 0ug, 10ug, and 40ug
- 4 of 12 mice died at 100ug dose
- Lack of hematology, blood chemistry, and histopathological abnormalities in surviving mice
- The NOAEL dose is $>10\text{ug}$ and $\leq 40\text{ug}$



Animal IV Trial Results

- Dose dependent expression of GNE transgene in mice following IV injection
- 75% of all tissues analyzed were positive for GNE transgene expression at 100ug dose



Rationale for IV Administration in Compassionate Subject

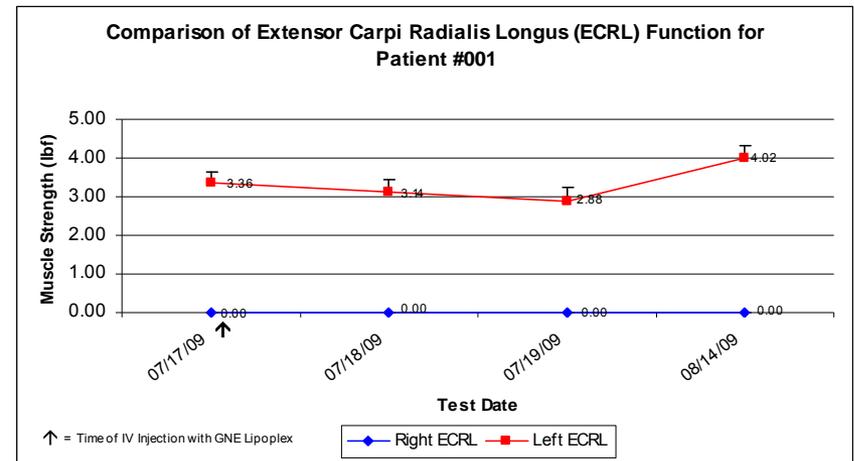
Thus, given...

- The subject's muscle function is deteriorating over time
- IM injection of 400ug of pUMVC3-GNE DNA lipoplex is safe and well tolerated
- Treatment has demonstrated transient direct and local regional muscle benefit
- The proposed dosing schema begins with a 400ug IV dose which is 1/400th of the IV NOAEL in mice
- We and others (Gahl) hypothesize that sialic acid may be produced outside of muscle and utilized by muscle alleviating symptoms of HIBM

**...the IV amendment was moved forward and approved
by FDA on June 25, 2009**

Results of Intravenous Administration in Single Patient

- No significant toxic effect except transient Grade 1 fever and Grade 2 headache
- Muscle function improvement in previously injected left ECRL noted



Future Plans

- Serum samples are being collected for cumulative analysis of sialic acid at the end of the study
- Current multi-injection IV safety, expression, and limited toxicity study (RE-PTL 113) in animals is ongoing (multiple organ analysis)*
- Biodistribution (RE-PTL 111) and toxicology (RE-PTL 112) studies are approved by animal safety committee at UNT^o
- Once database is complete, a Phase I intravenous protocol will be submitted

* Results critical for continuation of dose escalation. Plan re-discuss with FDA after 4 mg dose level (total being 5.8 mg)

^o Results critical for Phase I trial submission

