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Silencing of Growth Hormone Receptor by siRNA Ameliorated Disease in a Preclinical Rat Model of Acromegaly

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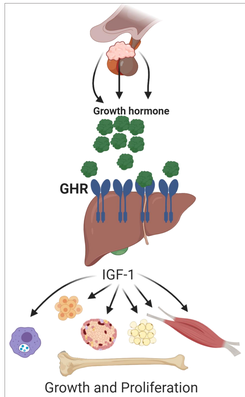
OBJECTIVE

Demonstrate ability of GalNAc-siRNA conjugate to resolve pathology in a preclinical animal model of acromegaly.

INTRODUCTION



https://themindcircle.com/andre-the-giant/

Acromegaly is a rare and chronic disease characterized by disproportionate skeletal, tissue, and organ growth due to the overabundance of growth hormone (GH) – usually attributed to the presence of a GH-secreting pituitary adenoma. Multiple therapies exist to modulate the excessive secretion of GH and the associated elevations in insulin growth factor-I (IGF-I), including surgery and radiation therapy directed at the adenoma and small molecule somatostatin analogs and growth hormone receptor (GHR) inhibitors to inhibit the downstream effects of excessive GH. Unfortunately, these approaches are often invasive or provide limited efficacy. siRNA-GalNAc conjugates delivered subcutaneously offer the potential for less invasive, more efficacious silencing of the GH pathway, either as standalone therapy or in combination with existing approaches to amerliorate disease.

RESULTS

Figure 1: Establishing a Rat Model of Acromegaly

Guided by published protocols, we established a rat model of acromegaly in house. This tumor-based model recapitulates clinically relevant symptoms, including weight gain and elevated serum IGF-1 levels.

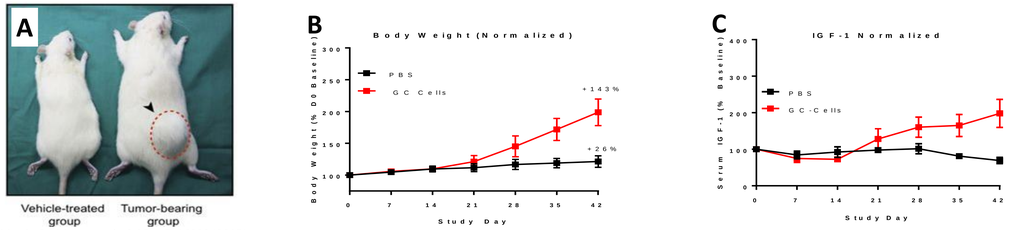


Figure 1: In-house recapitulation of rat model of acromegaly. (A) Taken from Martin-Rodriguez et al., demonstration of effect of tumor cell injection on rat size. **(B)** In-house modeling demonstrated the manifestation of clinically relevant features such as increased body weight and serum IGF-1 **(C)**.

Figure 2: GalNAc-siGHR Treatment Ameliorated Pathology

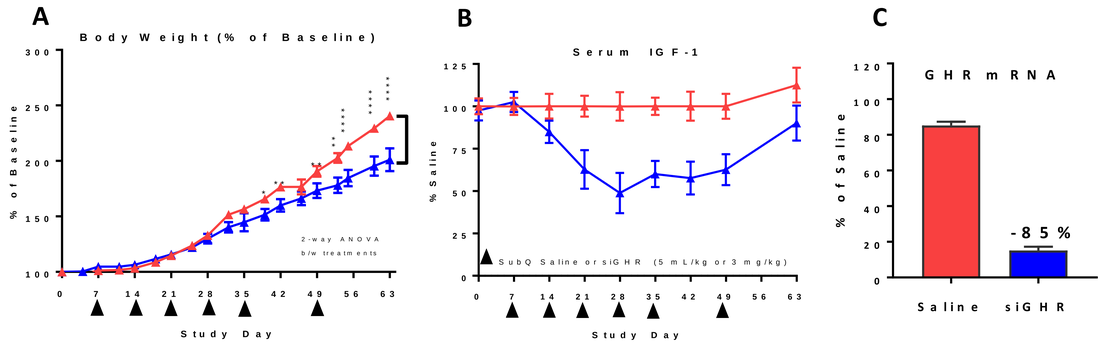


Figure 2: GalNAc-siGHR Treatment Ameliorated Clinically Relevant Symptoms of Acromegaly. Six doses of GalNAc-siGHR given at weekly and then biweekly intervals to rats exhibiting acromegaly symptoms significantly reduced body weight gain **(A)**, as well as serum IGF-1 **(B, Numerical values are presented in Table 1)**. Mechanism of action was confirmed in the analysis of terminal liver samples showing an 85% reduction in GHR mRNA **(C)**.

Table 1: GalNAc-siGHR Treatment Lowered Serum IGF-1

	Serum IGF-1 (ng/mL)					
Treatment	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63
Untreated (% Saline)	722 ± 139 (107%)	1169 ± 314 (110%)	955 ± 156 (110%)	970 ± 266 (107%)	1041 ± 243 (107%)	1059 ± 277 (104%)
siRNA (% Saline)	454 ± 259 (63%)	571 ± 438 (49%)	574 ± 237 (66%)	560 ± 300 (62%)	653 ± 298 (67%)	780 ± 329 (76%)

Table 1: Quantifying GalNAc-siGHR mediated decreases in serum IGF-1 levels. Serum IGF-1 is one of the main clinical parameters for monitoring acromegaly disease progression. Expanding upon Figure 2b, treatment of acromegaly rats with GalNAc-siGHR demonstrated a sustained decrease in serum IGF-1 with weekly dosing (3 mg/kg).

CONCLUSIONS

- GalNAc-siGHR reduced liver GHR expression by 85% and normalized IGF-1 expression
- Liver reduction of GHR affects GH signaling ultimately effecting a reduction in body weight.
- **Liver reduction of GHR was sufficient to normalize IGF-1 levels in the blood**
- Future Direction: Development of a clinical candidate and preclinical evaluation of safety and efficacy in an NHP model.

CONTACT INFORMATION

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