Oligonucleotide Mediated Upregulation of Serping1 By Targeting Regulatory RNAs

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# Upregulating Serping1 for treatment of Hereditary Angioedema

HAE is a life-threatening haploinsufficient liver disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
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| ▪ Primarily caused by mutations in *SERPING1* encoding C1-INH protein  
  ▪ Autosomal dominant  
  ▪ Loss of function  
  ▪ >250 causative mutations  
| ▪ *SERPING1* is expressed in the liver  
  ▪ Functions as a protease inhibitor  
  ▪ the inhibition of the complement system to prevent spontaneous activation  
  ▪ major regulator of contact activation |

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<th>Target Approach</th>
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<td>▪ Haploinsufficient diseases, such as HAE, are ideal cases for restoring levels via CAMP4’s upregulation platform</td>
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**C1-INH deficiency** leads to ↑ bradykinin (vasodilator peptide)

C1-INH

*Plasma inhibitor of FXIIa and Kallikrein*

FXIIa

Kallikrein

Pre-kallikrein

↑ Bradykinin

Bradykinin B2 Receptor

Edema

*Serping1 gene*  
*Increased mRNA expression*
RNA Actuating Platform (RAP™): Targeting regRNA to upregulate gene expression

1. Map regRNAs in Mouse livers via NGS techniques

2. Identify regRNA Hotspots via screening in Mouse Heps

3. Program for Druggability

First-pass Screen

92 ASOs

Optimize

42 ASOs

 Leads

3 ASOs
regRNA targeting ASOs upregulate Serping1 in vitro and in vivo

Primary Mouse Hepatocytes

Serping1

Wild-type Mice

Serping1 levels in serum with ASO treatment

- Fold-change is specific for target gene - effect not observed for neighboring genes
- Efficacy achieved with a 1.5-2X upregulation with ASOs occurring both in vitro and in vivo
Achieved Additivity for Serping1 with ASO and ligand combination

- Utilized a known ligand for Serping1 induction (Interferon gamma) to address regRNA inducibility

Proposed mechanism:

- Stimulation with IFN gamma in mouse hepatocytes and mouse livers lead to an increase in regRNA, followed by an increase in mRNA levels
- Treatment of IFN gamma in combination with ASOs targeting Serping1 regRNA leads to an additive effect in mouse hepatocytes
- Similar trend observed in wild-type mice
ASOs restore expression in haploinsufficient HAE setting

- Mimicking C1INH-deficiency in vitro: reducing Serping1 to 50% of normal levels

**Effect of Jak1 inhibitor in Mouse**

**Mouse Hepatocytes**

- Downregulation of Serping1 mRNA

**Mouse Livers**

- Serping1 levels in response to IFNg plus regRNA ASOs

- In HAE-like setting, ASO treatment upregulates Serping1
- Suggests RNA Actuators are capable of restoring healthy expression
Conclusion

• CAMP4’s RAP platform identified regRNA that can control Serping1 expression
• Identified multiple ASOs targeting the regRNA, that can upregulate the gene expression
  • In mouse hepatocytes
  • In mouse livers
• Provides a novel approach to treat HAE
• The platform provides unique approach to upregulate endogenous gene expression in a tunable manner and illustrates application for a broad range of diseases.