



Oligonucleotide Mediated Upregulation of Serping1 By Targeting Regulatory RNAs

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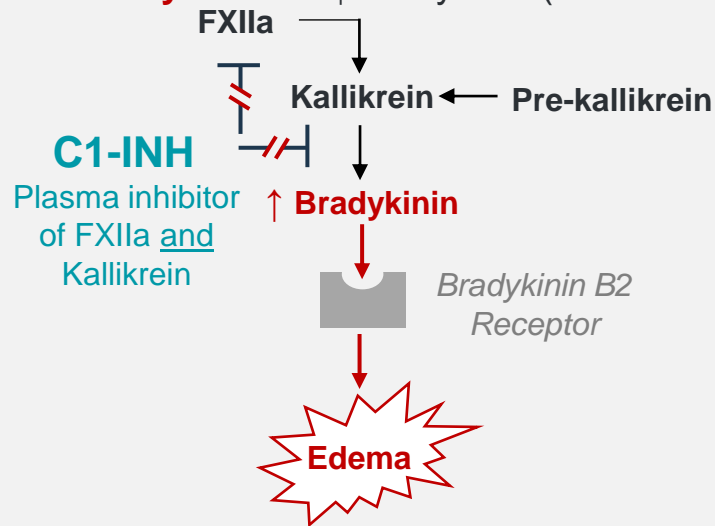
CAMP4 Therapeutics, Cambridge, MA

Upregulating Serping1 for treatment of Hereditary Angioedema

HAE is a life-threatening haploinsufficient liver disease

Disease

- Primarily caused by mutations in *SERPING1* encoding C1-INH protein
 - Autosomal dominant
 - Loss of function
 - >250 causative mutations
- C1-INH deficiency** leads to ↑ bradykinin (vasodilator peptide)

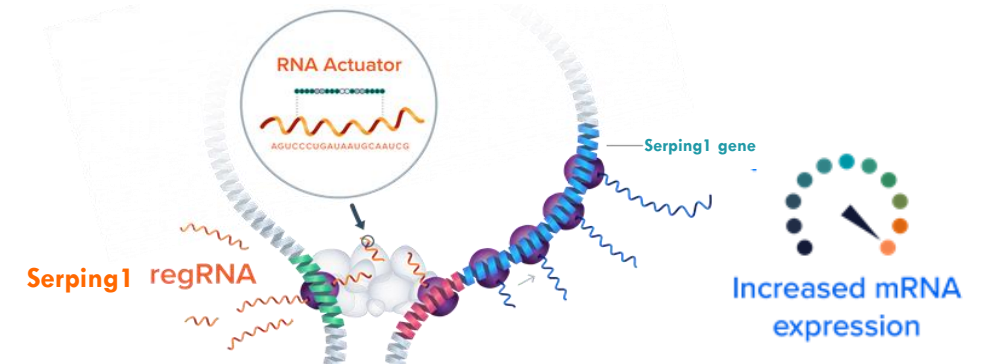


Gene

- 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

Target Approach

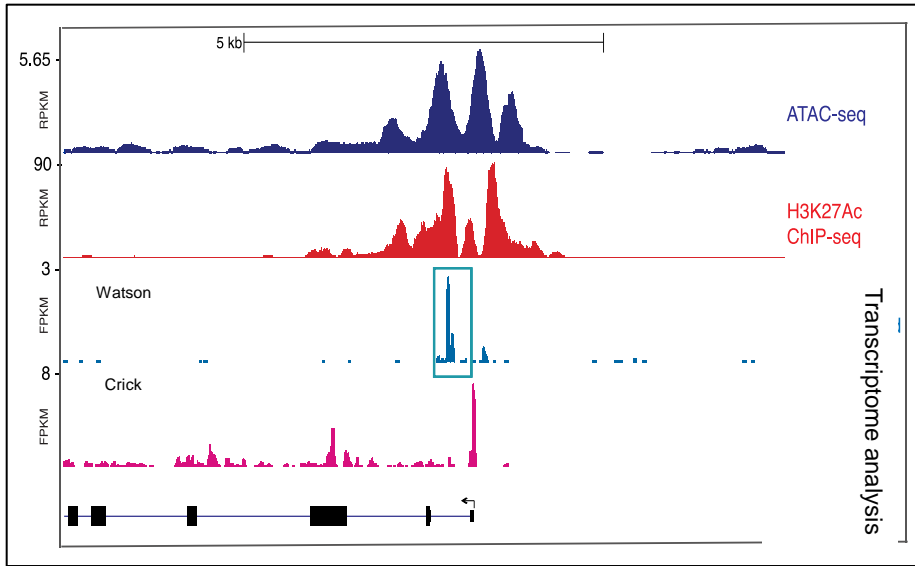
- Haploinsufficient diseases, such as HAE, are ideal cases for restoring levels via CAMP4's upregulation platform



RNA Actuating Platform (RAP™): Targeting regRNA to upregulate gene expression

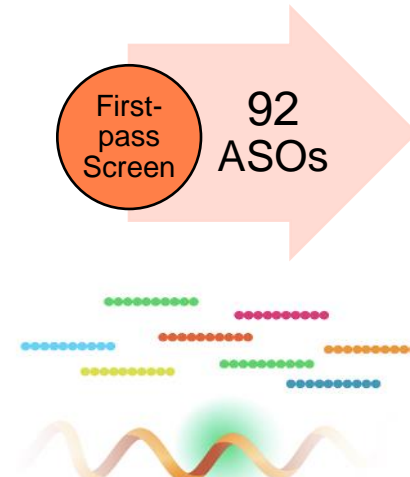
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Map regRNAs in Mouse livers via NGS techniques



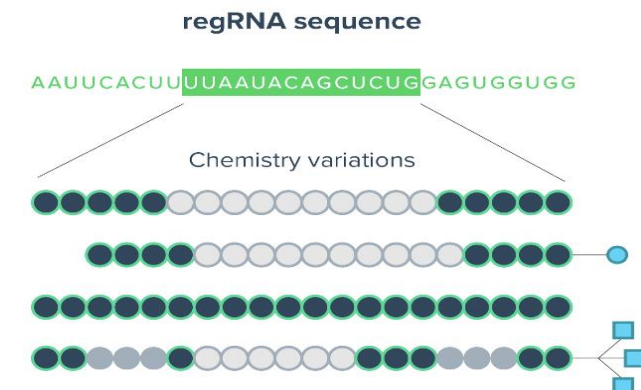
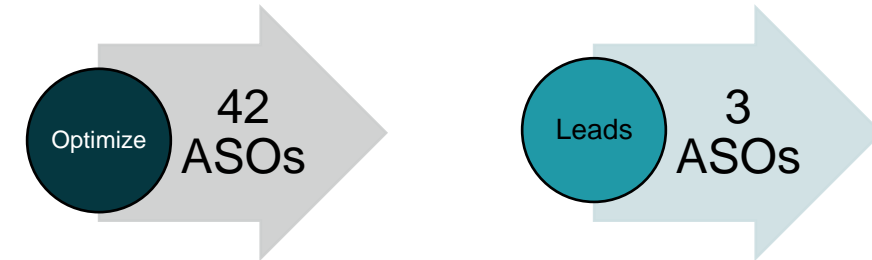
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Identify regRNA Hotspots via screening in Mouse Heps



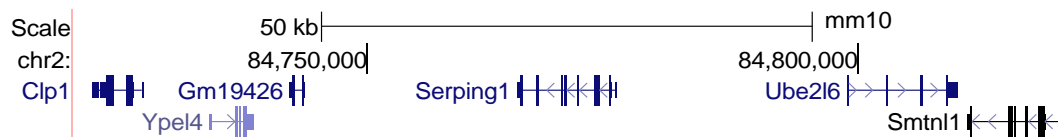
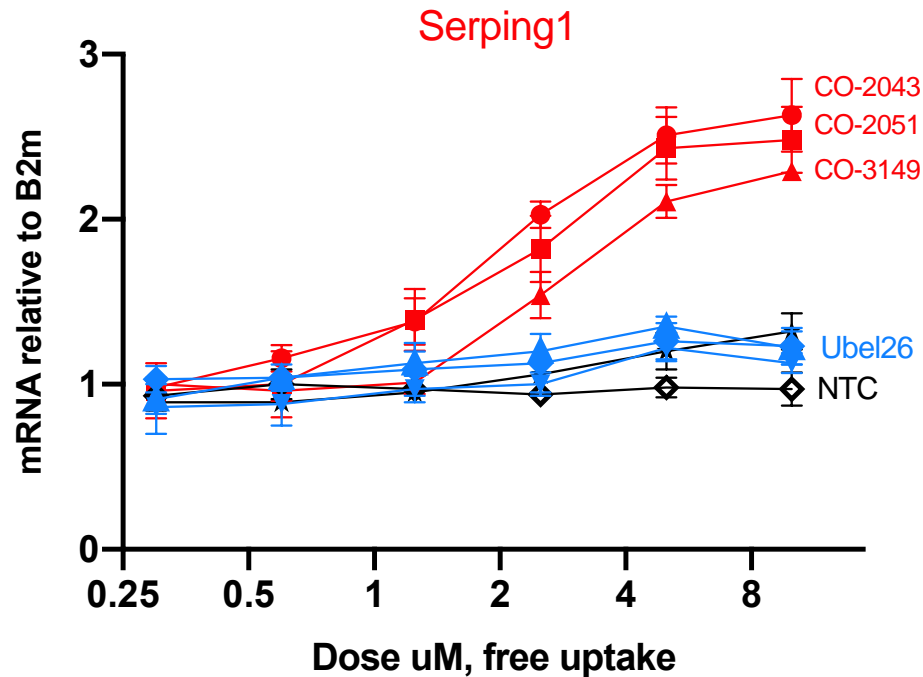
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Program for Druggability



regRNA targeting ASOs upregulate Serping1 in vitro and in vivo

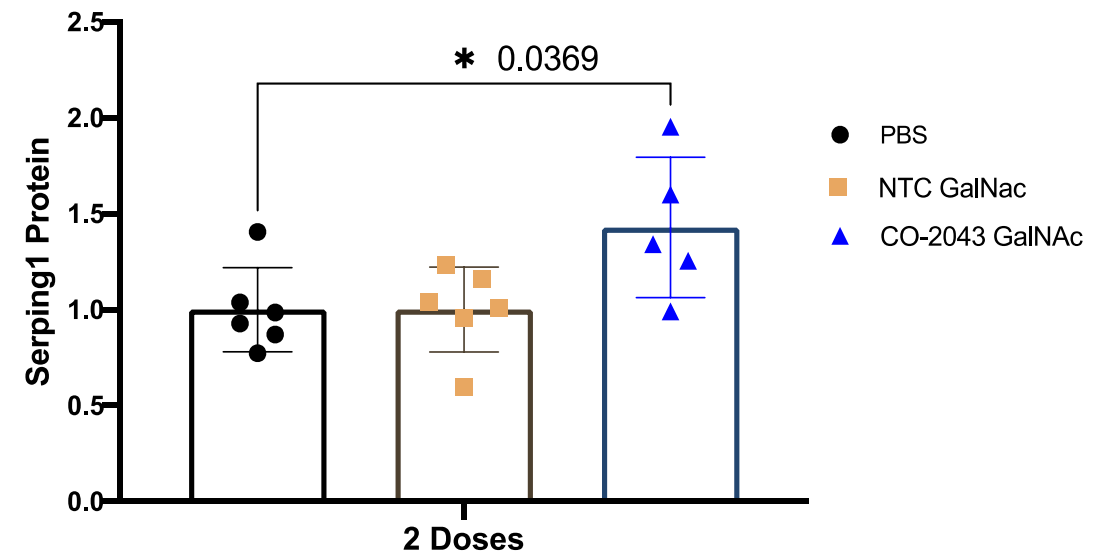
Primary Mouse Hepatocytes



- 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

Wild-type Mice

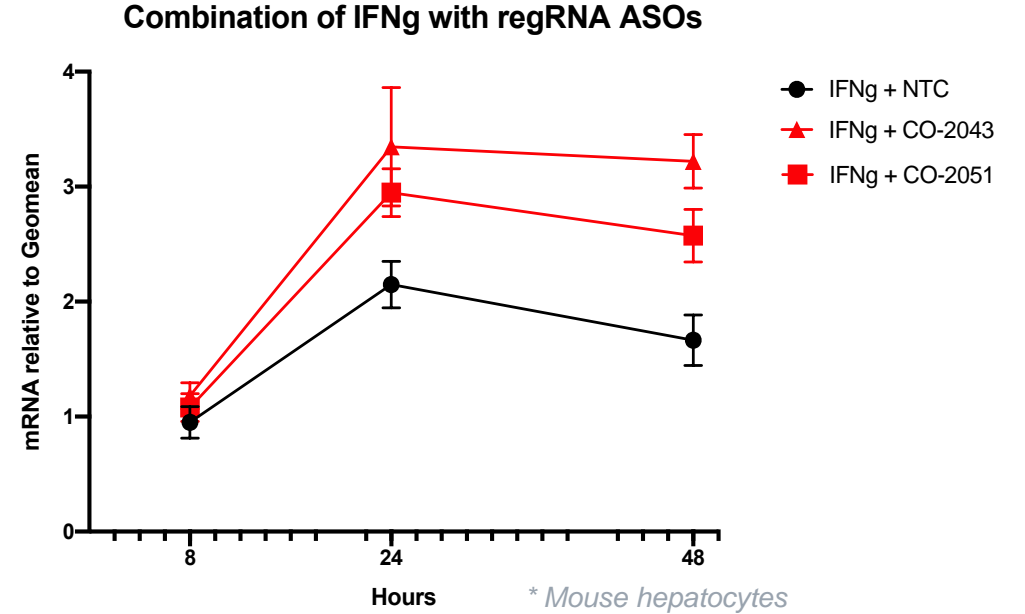
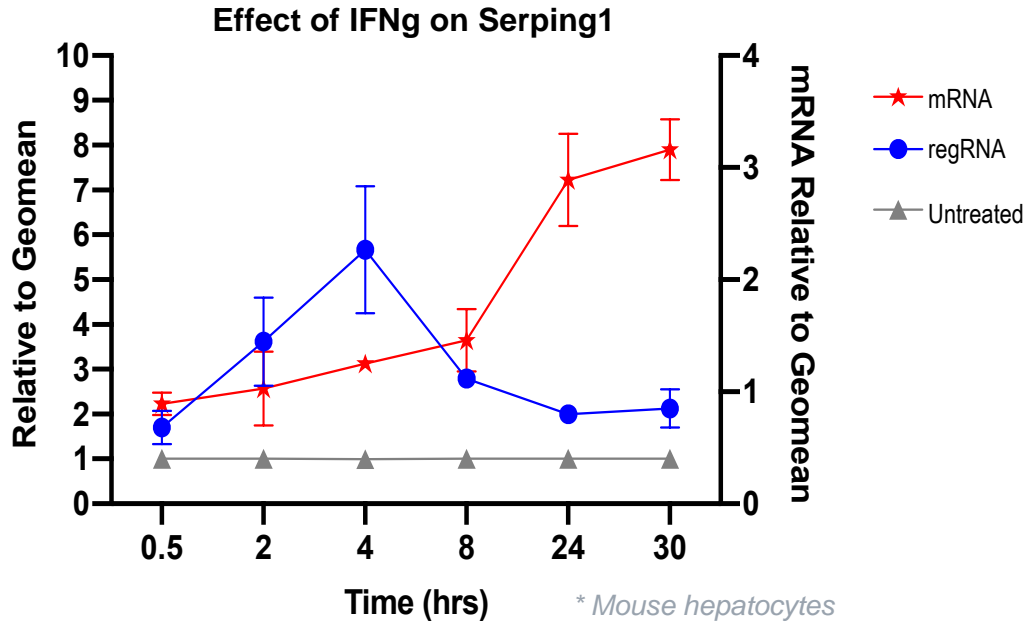
Serping1 levels in serum with ASO treatment



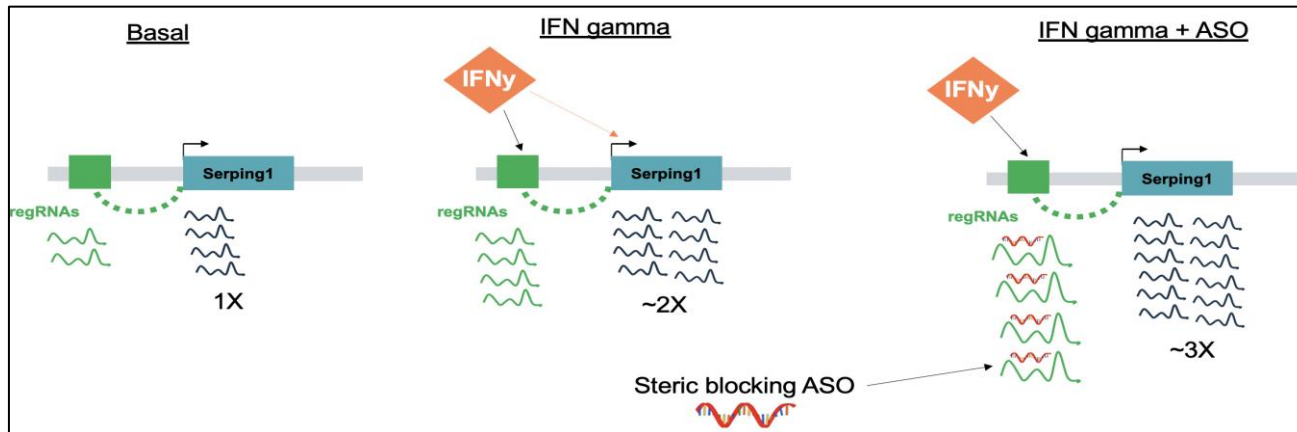
- Male C57/Bl6 mice, ~8 weeks age
- Subcutaneous injection (ASO)
- 48hrs post dose serum collection

Achieved Additivity for Serping1 with ASO and ligand combination

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



Proposed mechanism:



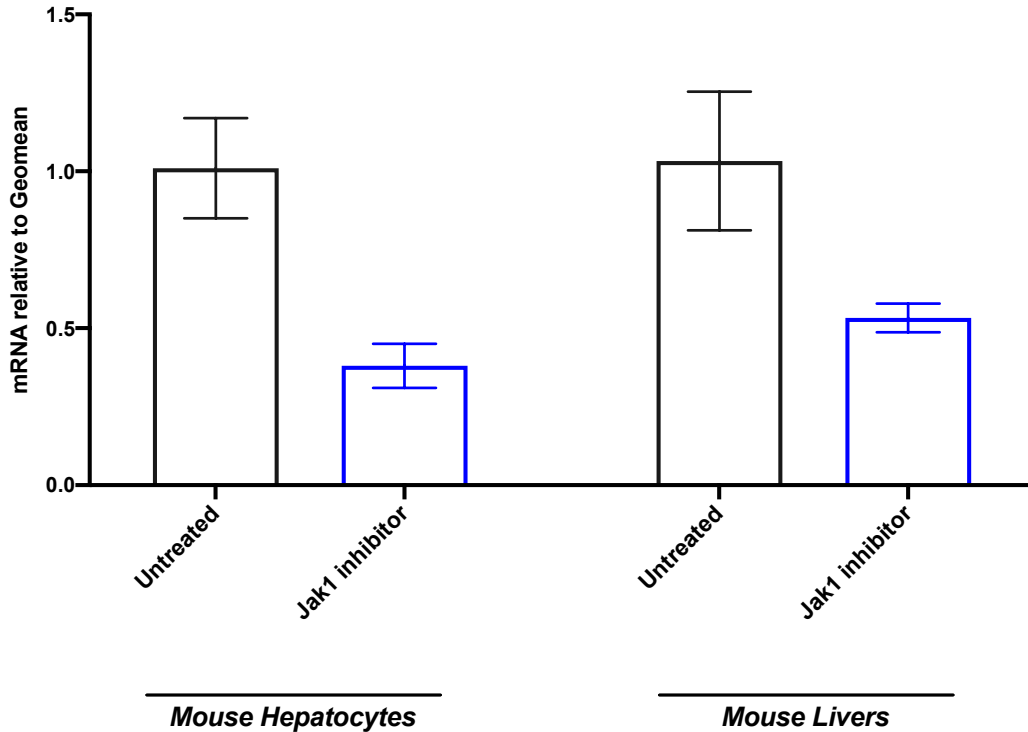
- Stimulation with IFN gamma in mouse hepatocytes and mouse livers lead to an increase in regRNA, followed by an increase in mRNA levels
- Treatment of IFN gamma in combination with ASOs targeting Serping1 regRNA leads to an additive effect in mouse hepatocytes
- Similar trend observed in wild-type mice

ASOs restore expression in haploinsufficient HAE setting

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

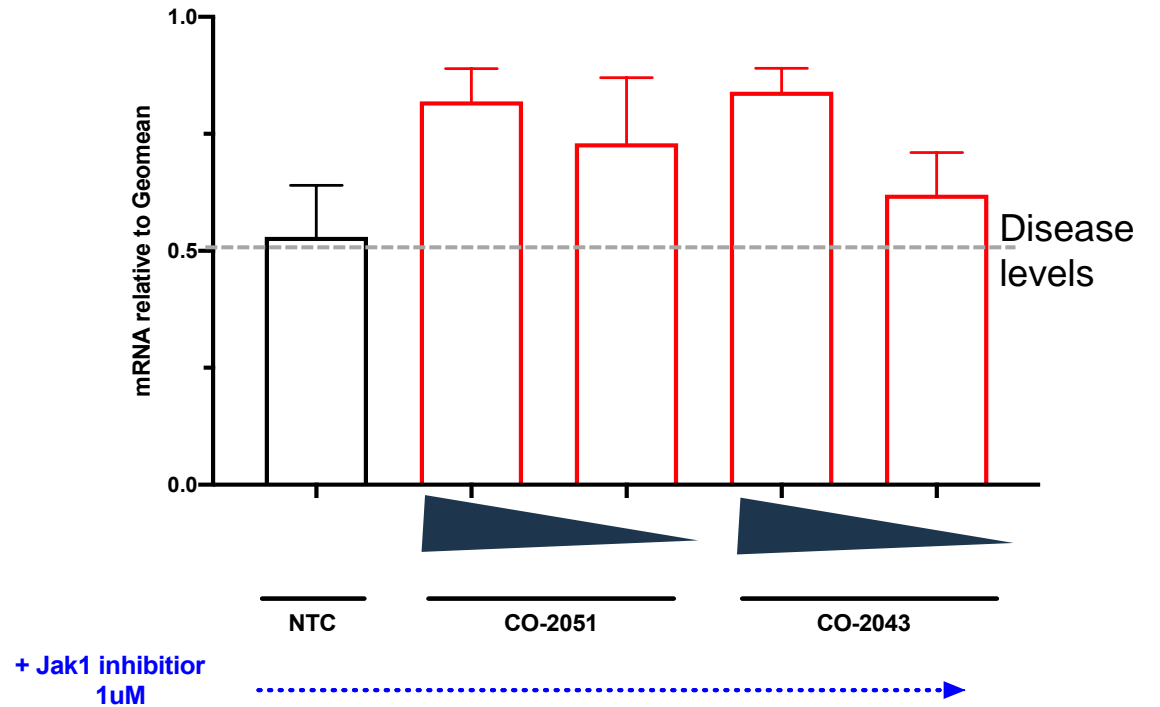
Effect of Jak1 inhibitor in Mouse

Downregulation of Serping1 mRNA



Mouse Hepatocytes

Serping1 levels in response to IFN γ 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.