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Development of a Next Generation Synthetic Promoter for Liver Directed Gene Therapy

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Forward-looking Statements

This presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as “anticipate,” “believe,” “could,” “estimate,” “expect,” “goal,” “intend,” “look forward to,” “may,” “plan,” “potential,” “predict,” “project,” “should,” "will,” “would” and similar expressions. Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this press release. These forward-looking statements include, but are not limited to, statements regarding the development of our gene therapies, the success of our collaborations, and the risk of cessation, delay or lack of success of any of our ongoing or planned clinical studies and/or development of our product candidates. Our actual results could differ materially from those anticipated in these forward-looking statements for many reasons, including, without limitation, risks associated with collaboration arrangements, our and our collaborators’ clinical development activities, regulatory oversight, product commercialization and intellectual property claims, as well as the risks, uncertainties and other factors described under the heading "Risk Factors" in uniQure’s Quarterly Report on Form 10-Q filed on August 8, 2018. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, and we assume no obligation to update these forward-looking statements, even if new information becomes available in the future.

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Introduction

- *The AAV genome is 4.7kb*
  - *Gene therapy replace native genes of AAV with a new GOI*
- *Selection of promoter influenced by:*
  - *Cassette size*
  - *Expression level required*
  - *Off target expression – (tissue specificity)*
  - *Producibility/manufacturability*
- *Typically promoters selected for gene therapy have a native or viral origin*
  - *Native promoters are generally weaker and larger*
  - *Viral promoters have lower specificity and reliability*

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Introduction

- *Early liver specific promoters in gene therapy*
  - *Based on highly secreted liver proteins*
    - *Human serum albumin & α-1-antitrypsin (Kuriyama et al, Cell. Struct Funct, 1991)*
- *Chimeric promoters*
  - *Modular building block approach*
  - *Combining elements from ApoE, AAT, AMBP, TBG and WPRE*
- *Next generation promoters*
  - *Utilize in silico analysis of microarray data to identify liver specific control elements (Chuah et al., Mol Ther, 2014)*

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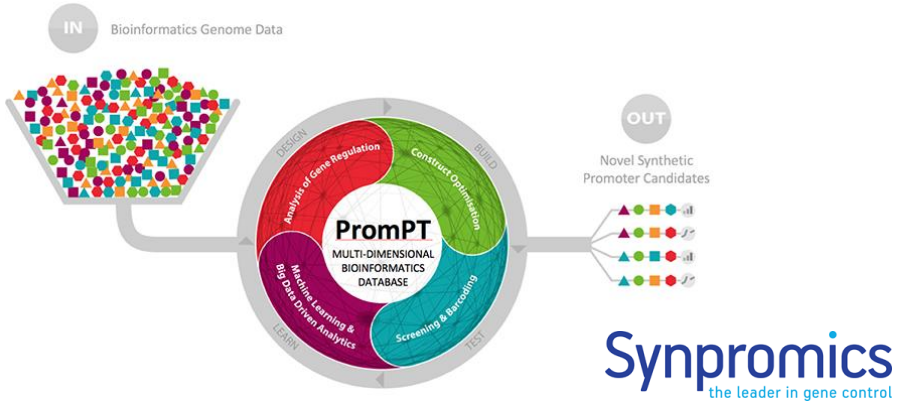
Collaboration with Synpromics

- *Identified need for a next generation promoter for our liver portfolio*
  - *Small, high tissue specificity and with broad indication application*
- *Synpromics utilizes proprietary technologies to develop synthetic promoters*
  - *This allows tailored promoters driving gene expression at desired levels and specificity*



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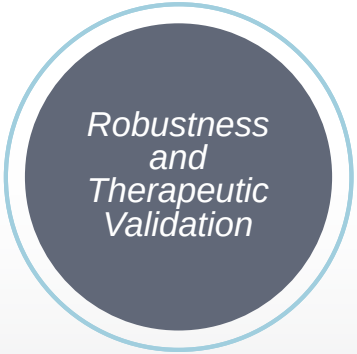
Technology Development

- *Liver specific libraries plus data driven rational promoter designs*
- *Promoters screened driving a reporter gene*
  - *Huh7, HepG2, HepaRG, prim. Hep*
  - *Off-target expression*
- *Selection of promoters*

- *Iterative rational design optimization*
- *Transfection and transduction with reporter (SEAP)*
- *In vivo study in mice*
  - *Activity*
  - *Tissue specificity*



- *50 promoter variations created for top 3 selected promoters*
- *Deletions, insertions, shuffling, variations, introns*
- *In vitro reporter assay*
- *Validation with therapeutic transgene in large animal model*

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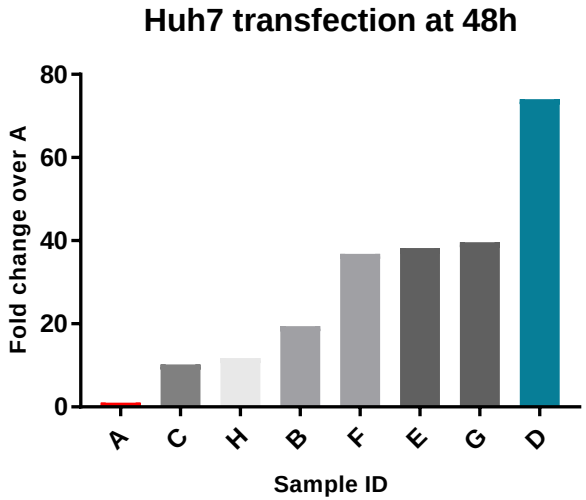
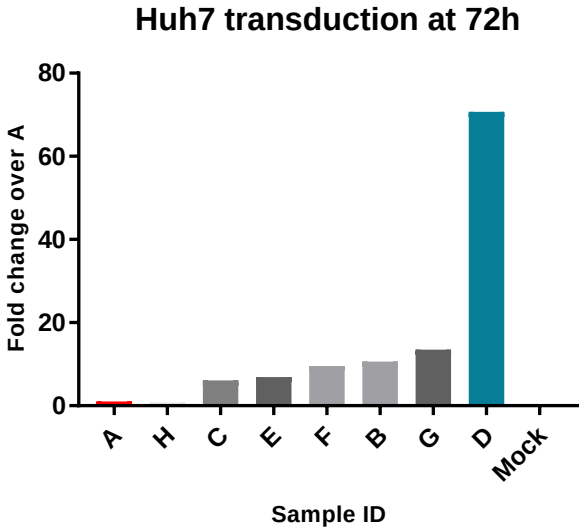
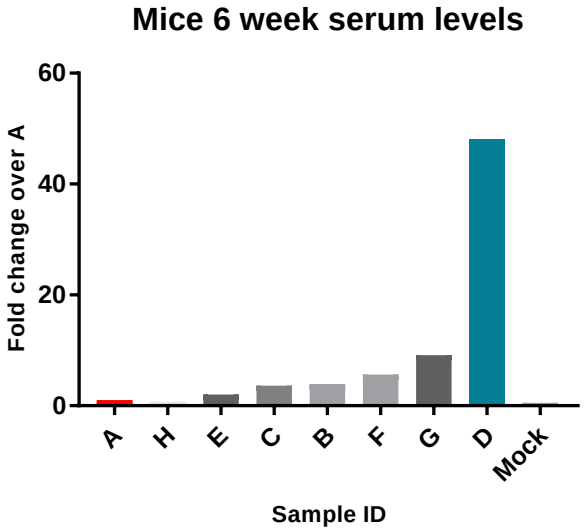
Transfection vs Transduction vs *in vivo*







- *In total 15 promoter designs were tested*
- *HepaRG, HepG2 and primary hepatocytes*
- *In vitro studies performed with biological and technical triplicates*
- *In vivo study performed with 5 mice per group. Mock = vehicle*
- *Promoter **D** robustly drove expression more than **40-fold** stronger compared to **A***
- *Lead promoter has less than 5% off-target expression relative to CMV*

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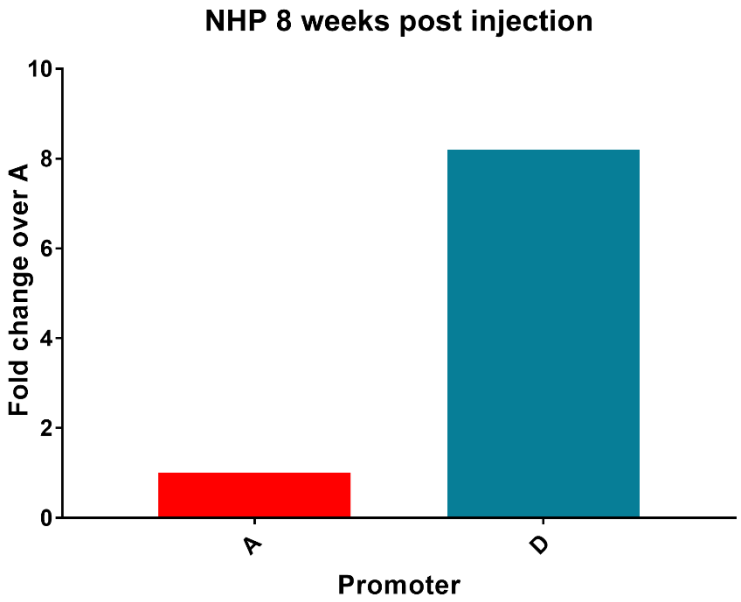
Therapeutic transgene validation in NHP

- *Expression of therapeutically relevant protein in NHP's*
- *Promoter D was selected to drive high levels of expression*
  - *Maintaining **8-fold** higher protein levels over reference promoter 8 weeks post-injection*
- *Part of ongoing study*

Note: promoter performance is transgene specific



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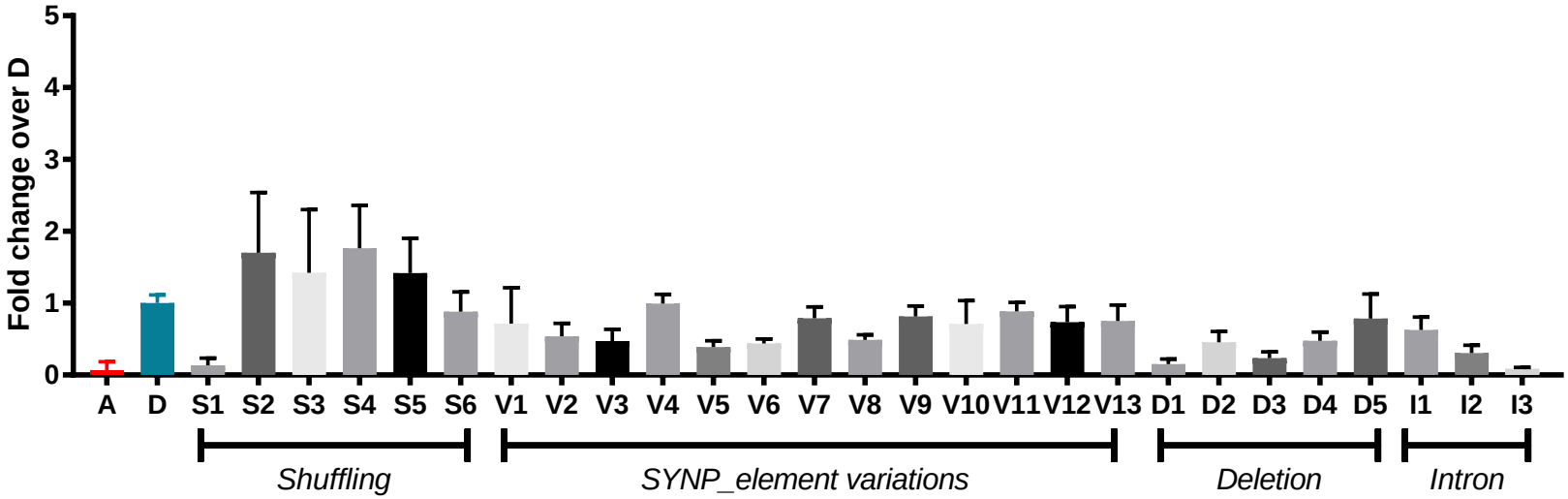
Promoters demonstrate robust activity



- *Top 3 selected promoter constructs unperturbed by derivation modifications*
- *No modification added significant improvement – robustness of promoter*

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Concluding remarks

Collaboration very successful in finding a synthetic promoter/s with the following attributes:

- *Majority smaller than 250bp*
- *More than 5-fold improvement in expression relative to reference promoter*
- *Validated in a large animal model with a therapeutically relevant protein*
- *Limited off-target expression**
- *Broad liver indication application*
- *Toolbox of promoters with varying levels of expression*

Exceptionally valuable instrument to drive the next wave of liver targeted gene therapy programs

Acknowledgements

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