# Scientific Poster Session

n-lorem FOUNDATION

## Nano-rare Patient Colloquium 2025

**Monday, October 20 | 5:15 – 6:15 pm EST**

### Progress in Creating Agonist-like ASOs for Patients with LOF Mutations

Building on foundational work from the Crooke lab and integrating our own AI-driven algorithm, we have developed a platform to identify and validate genomic regulatory elements that can be targeted by ASOs to upregulate protein expression. This therapeutic strategy has now established proof of concept protein upregulation and addresses haploinsufficiency and loss-of-function diseases through a mutation-independent approach, broadening its applicability across diverse patient populations.

**Anthony Vu, Ph.D.**

Assistant Director, ASO Strategy Research, n-Lorem


*Hosted by:*

Biogen

# Limitation of Current Therapies

- ~40% of approved drugs are **antagonists**
  - Designed to block overactive or toxic proteins

- **Unmet need**: many genetic disorders caused by too little protein (loss-of-function, LOF mutations)

- ~50% of therapeutic candidates currently rejected due to LOF

# A Novel Approach – Boosting the Good Copy

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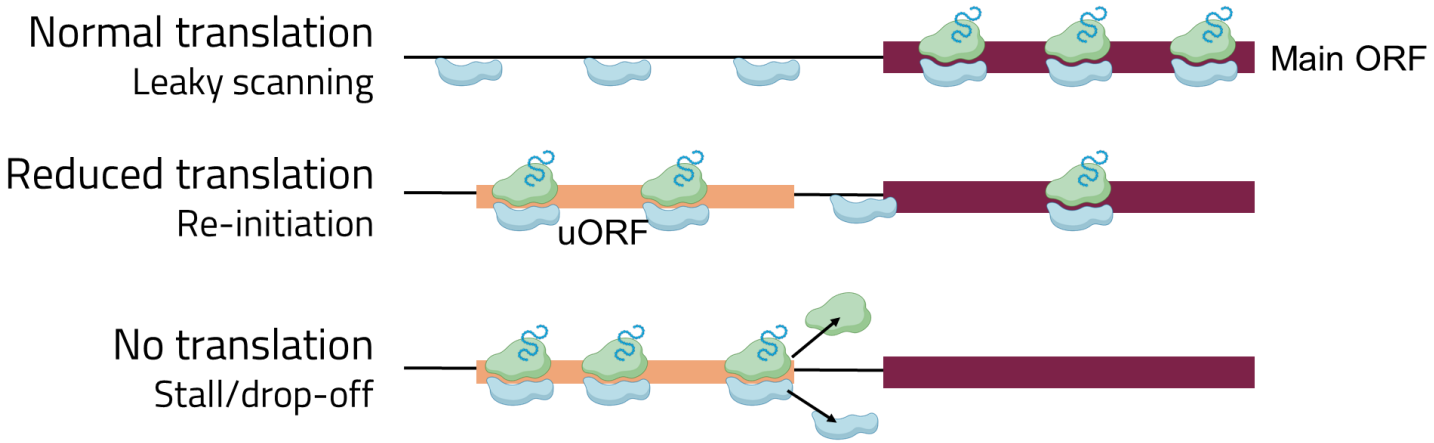
# A Novel Approach – Boosting the Good Copy

- **Haploinsufficiency**: one working copy of a gene produces insufficient protein
- **Therapeutic strategy**: upregulate expression from the wild-type allele
- **uORFs** (upstream open reading frames):
  - Found in the 5'UTR of many genes
  - Can **repress translation** of the main protein
  - Only a subset are functionally repressive → potential therapeutic targets



# From Discovery to Proof-of-Concept

- **Developed a pipeline** to find repressive uORFs

- **Case study**: DYRK1A haploinsufficiency
  - Causes a severe neurodevelopmental disorder
  - Validated uORFs with reporter assays
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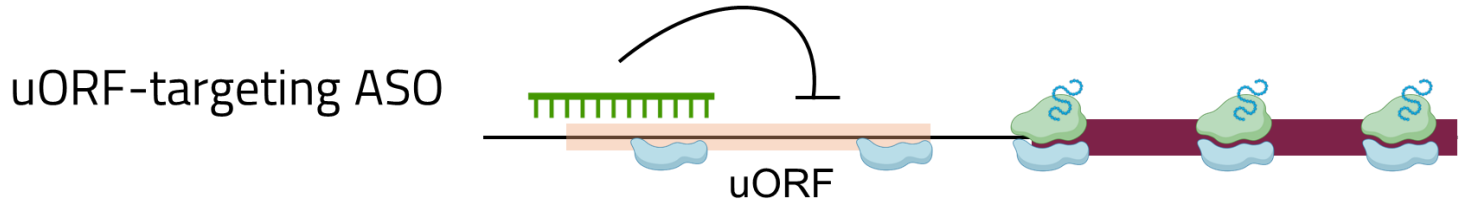
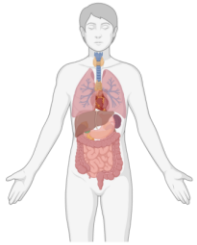
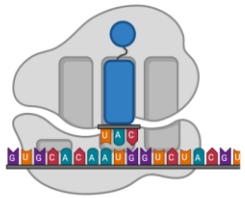



- **Result**: Blocking uORFs → **increase** DYRK1A protein

# Genome-wide identification of tissue specific uORFs



Tissue specificity



Ribosome profiling

In silico uORF prediction

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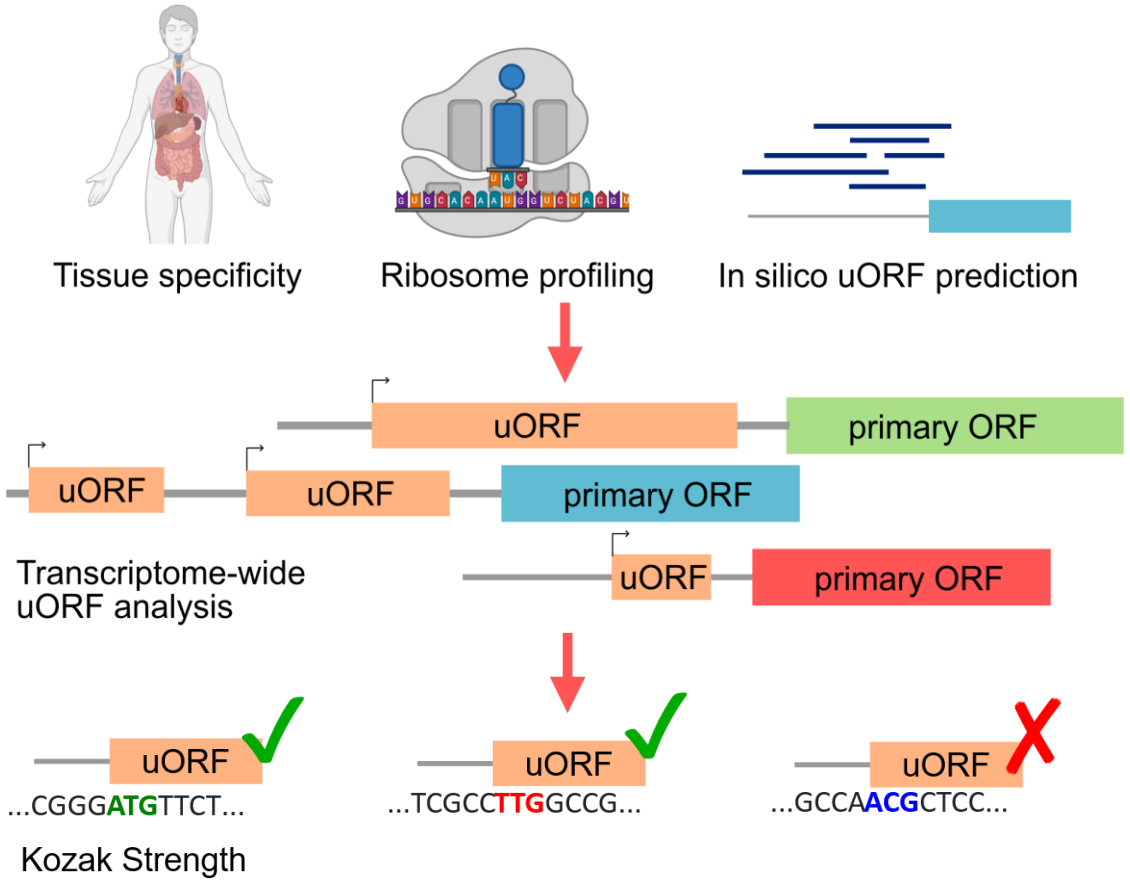
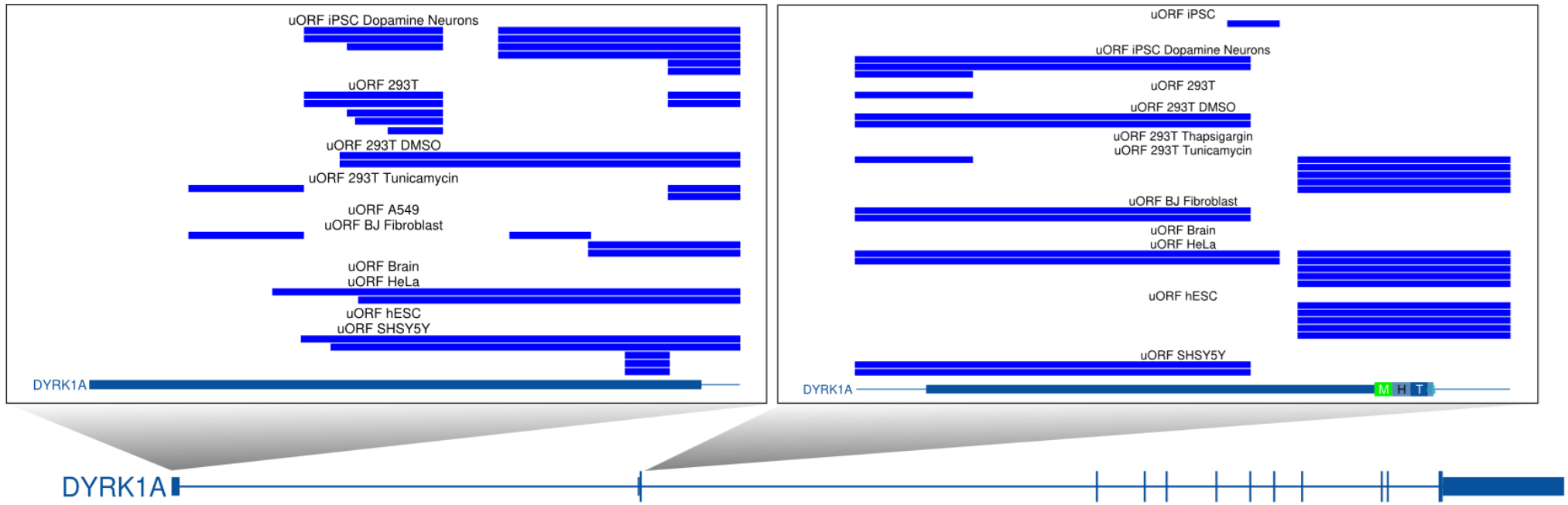
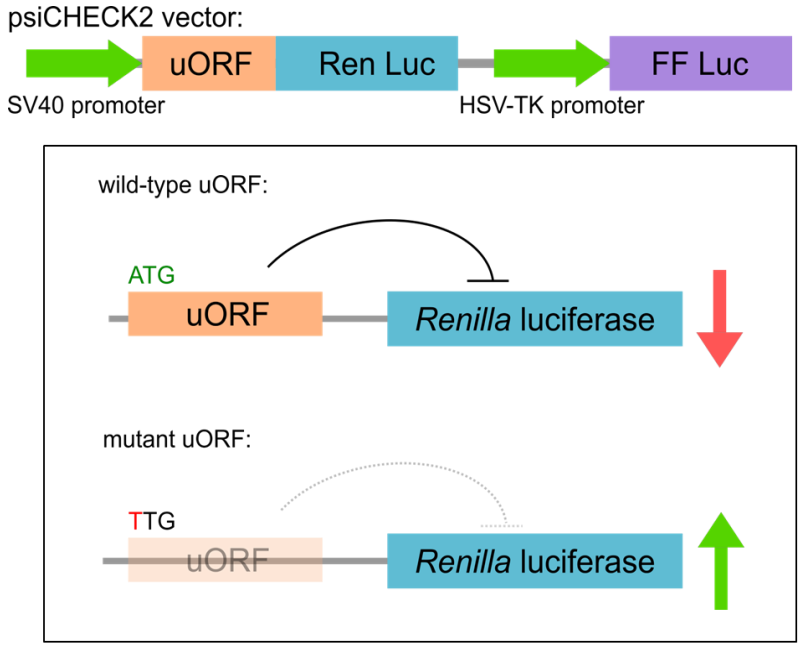


# Identification of DYRK1A uORFs



# Reporter-based functional validation of DYRK1A uORFs




1) Liang, Xue-Hai et al., *Nature biotechnology* (2016)

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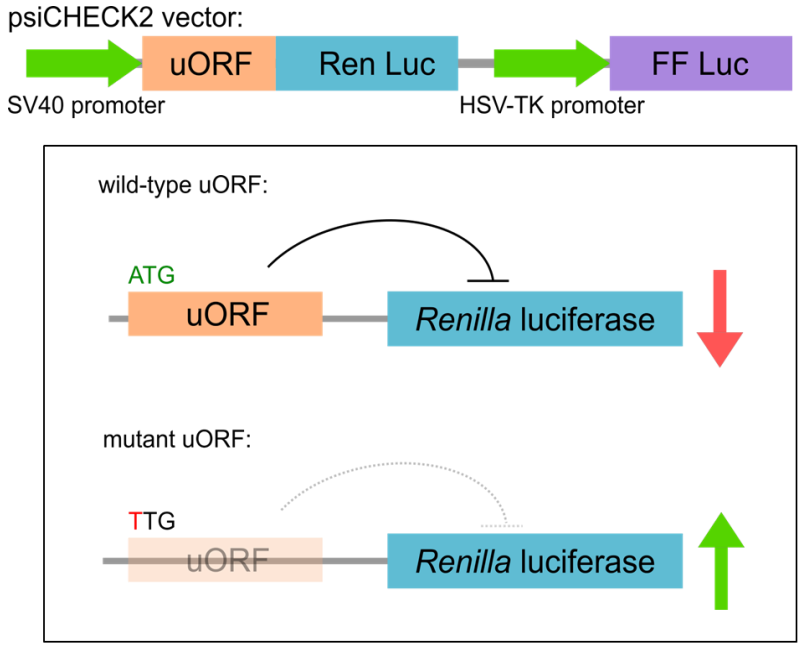


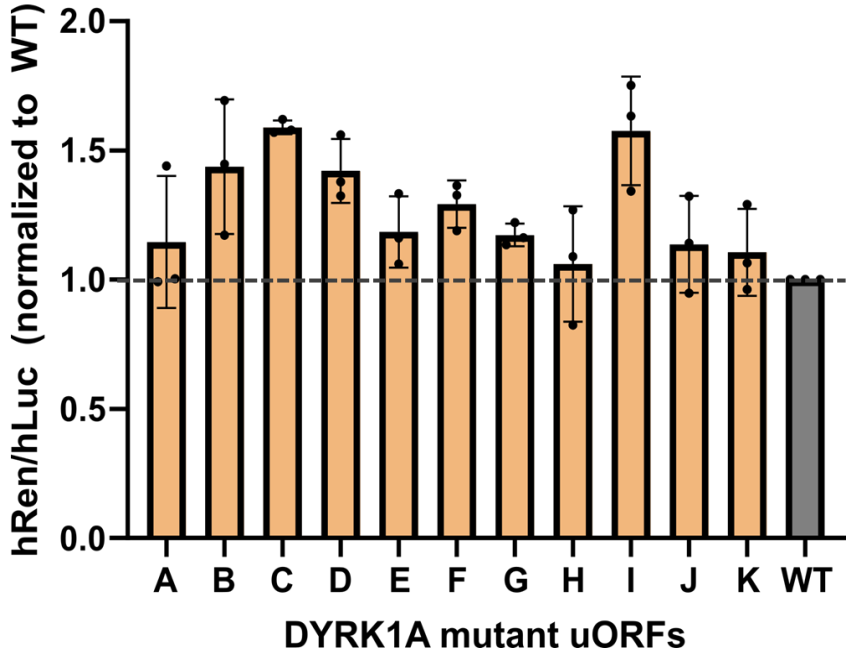


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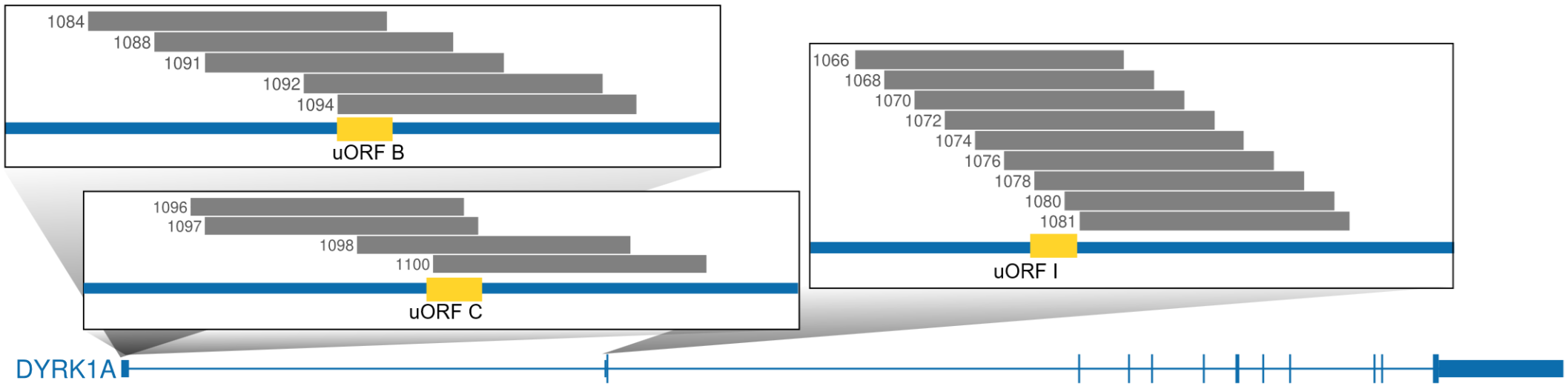
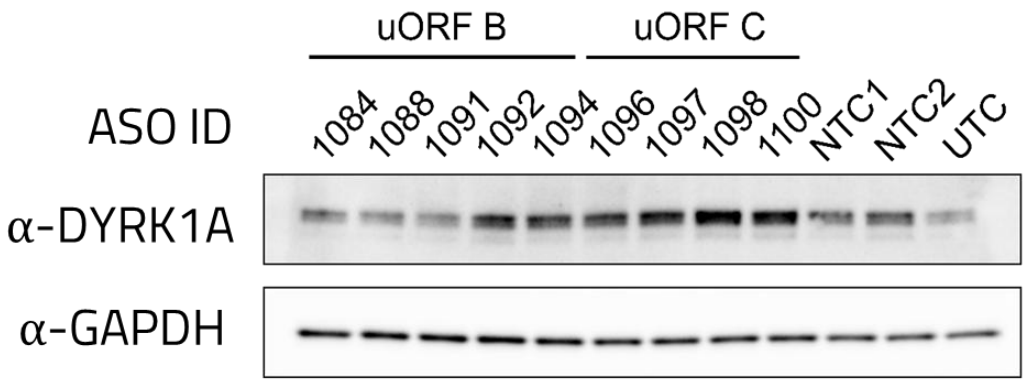
# Microwalk ASOs across uORFs




- ASO Design: Steric-blocking ASOs (fully 2’-O-methoxyethyl (2’-MOE)

# DYRK1A protein upregulation with uORF-targeting ASOs



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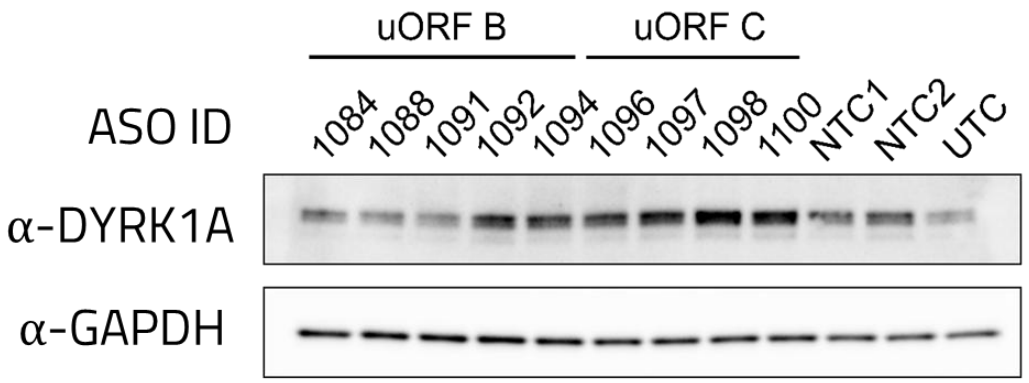
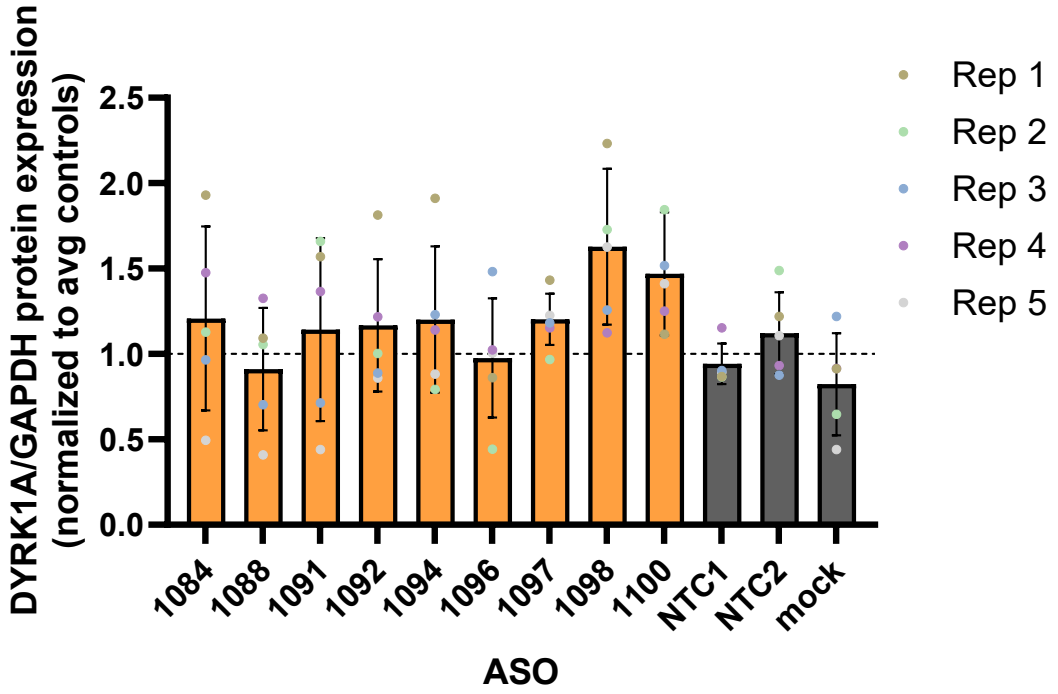
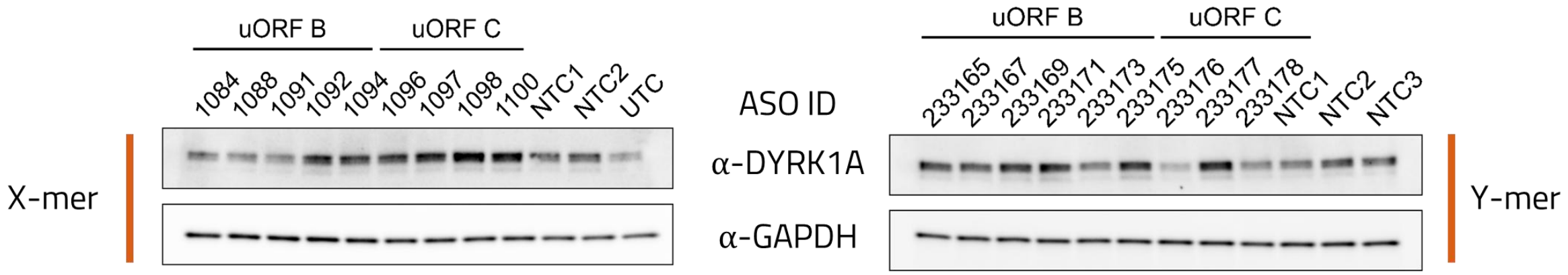


# Optimization of ASO length and dose



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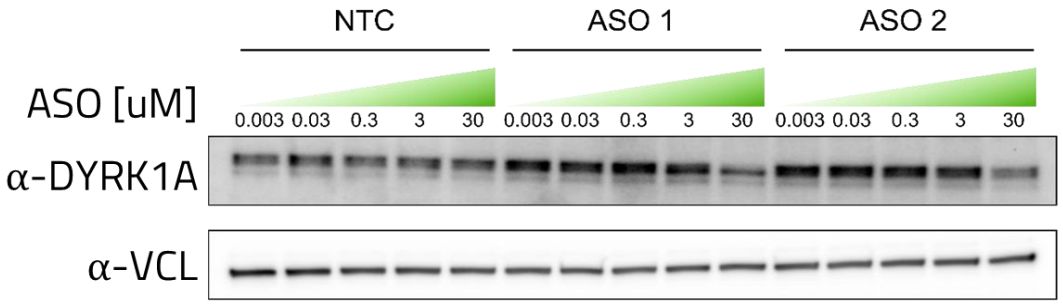


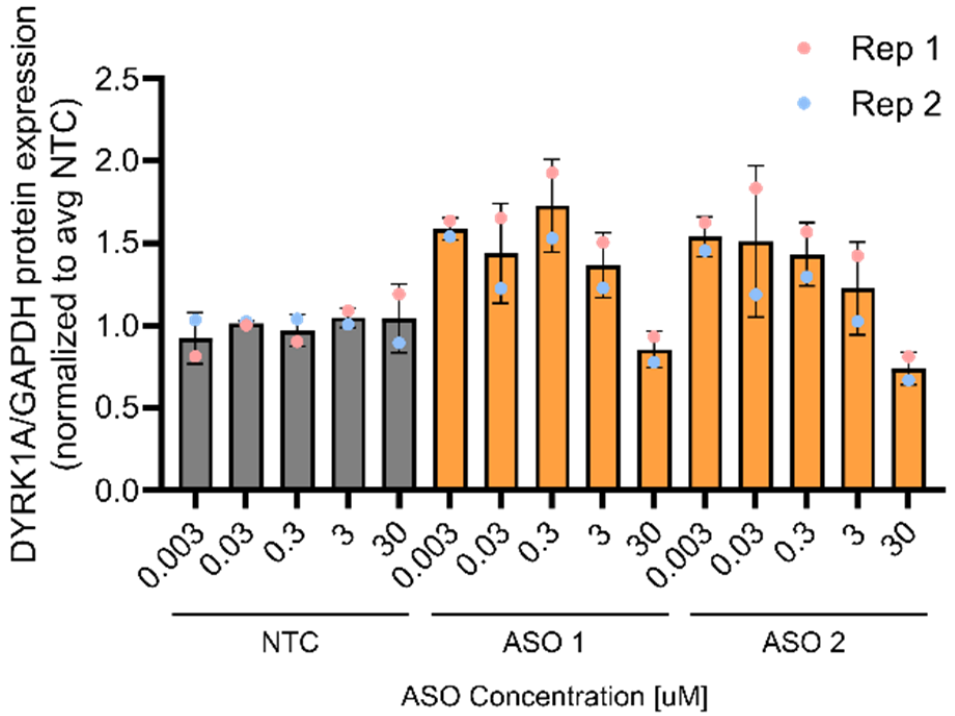

# Conclusion

Agonist-like ASOs: A New Therapeutic Strategy

- ASOs can block repressive uORFs to restore protein expression
- Genome-wide mapping reveals **tissue-specific uORFs** as therapeutic targets
- DYRK1A proof-of-concept:
  - Reporter assays + ASOs confirm uORFs inhibition **increases** protein expression
  - “Microwalk” approach shows **position-dependent activity**
  - Optimized ASO length to increase endogenous DYRK1A protein expression in the **nanomolar scale**

# Acknowledgements

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Thank you

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