A Novel Treatment Approach For Treating OTC Deficiency By Targeting RegRNAs Using Oligonucleotides

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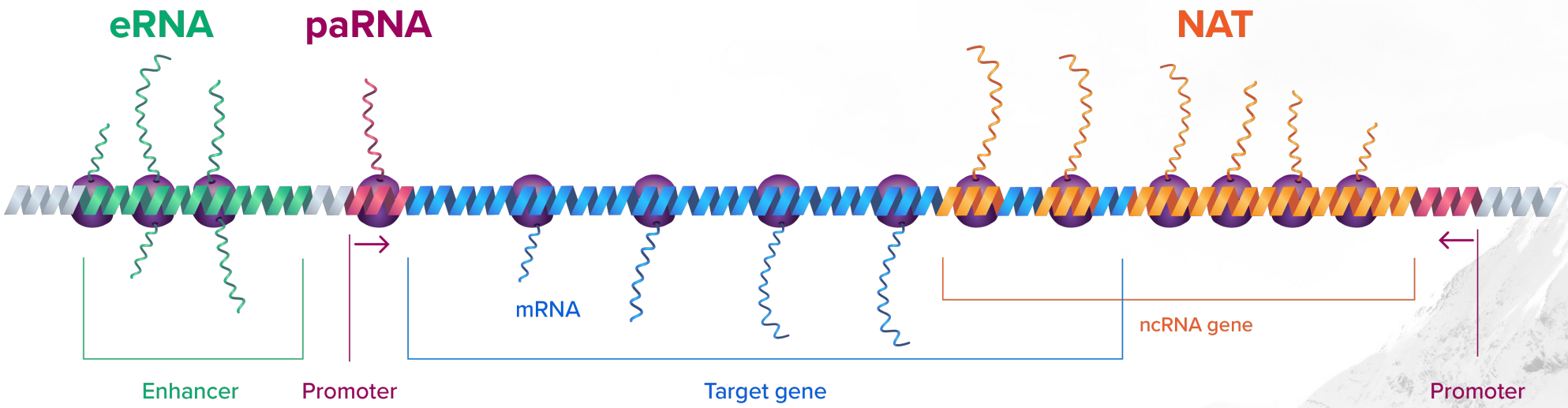
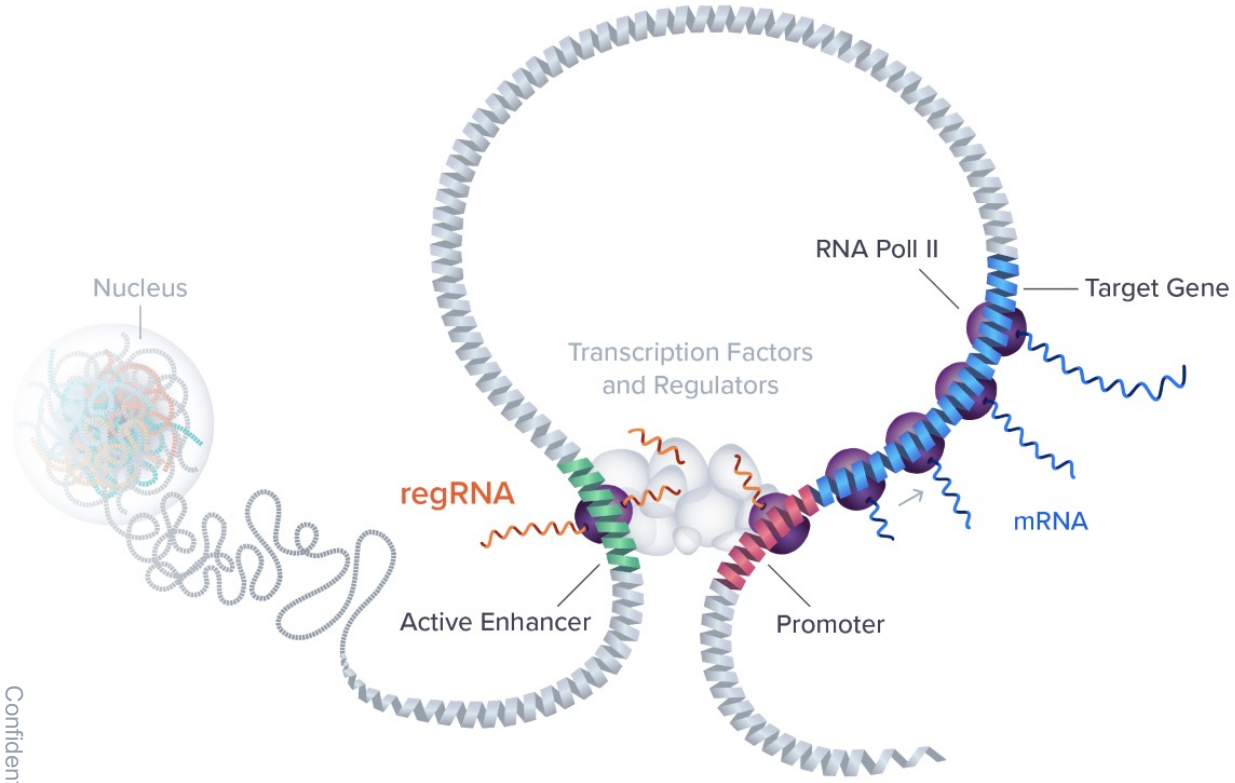
CAMP4 is pioneering the field of regulatory RNAs to upregulate genes



regRNAs are key controllers of gene expression



In the nucleus, genes and their regulatory elements are organized into conserved 3D DNA structures known as Insulated Neighborhoods to control gene expression.

regRNAs are uniquely transcribed within neighborhoods and act as rheostats for precise genomic control.

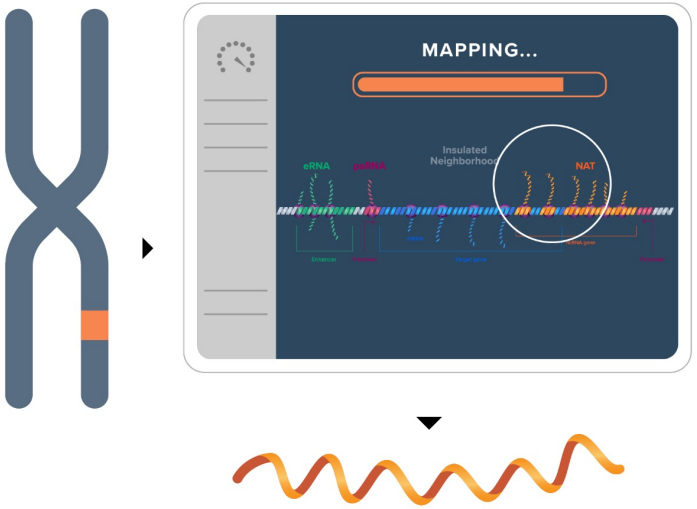
CAMP4 has created the only platform to drug regRNAs.

RNA Actuating Platform charts a proprietary path from RNA targets to drugs

1

Map regRNAs

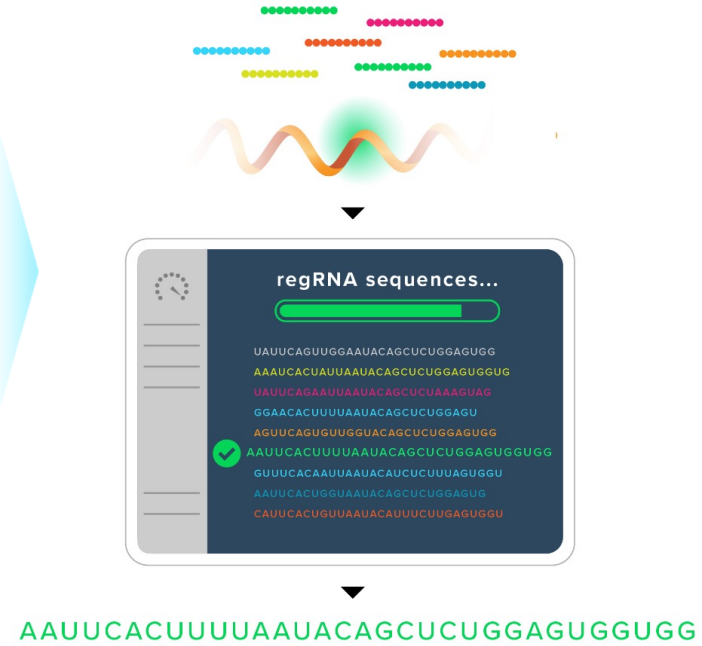
Next-gen sequencing powered by proprietary AI to identify regRNAs



2

Screen RNA Actuators

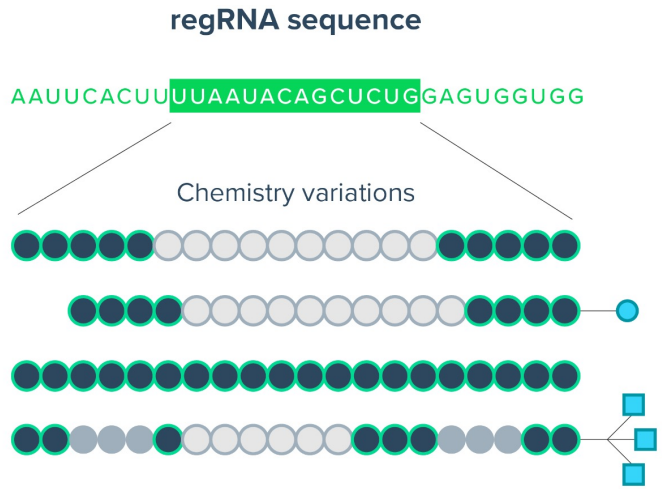
Screen oligo drug candidates to target regRNA hotspots for maximum gene upregulation



3

Program for Druggability

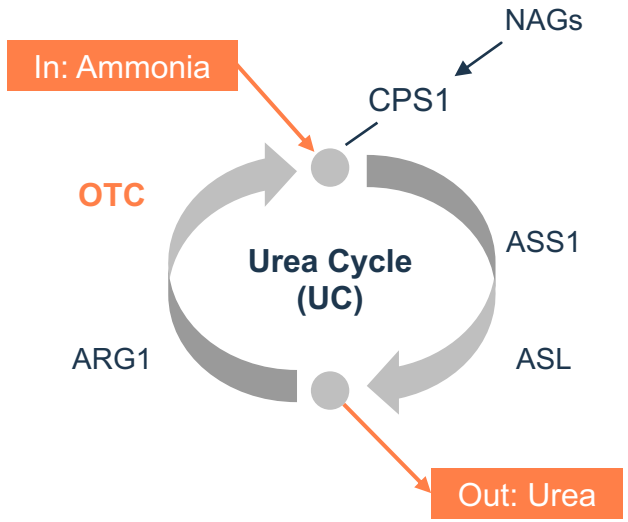
Design high-potency RNA Actuators for safe and effective delivery to target tissues underlying disease



Elevating residual OTC activity by at least 2-fold addresses 90% of patients

OTC Deficiency: largest subsegment of UCD patient population (50%)

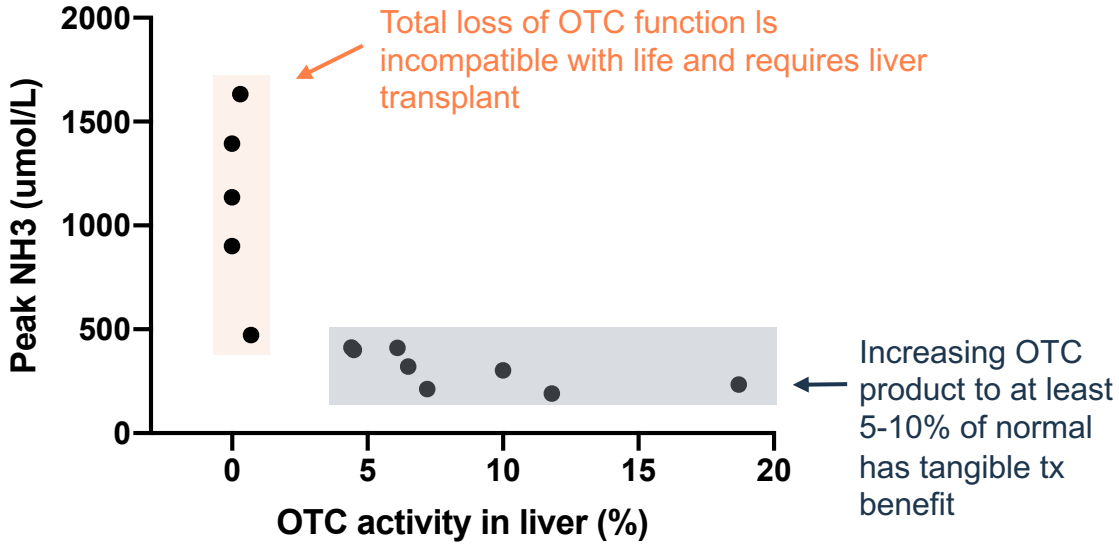
- Primary function of Urea cycle is detoxification of ammonia to urea for elimination
- Disease severity and age of onset varies with residual OTC activity and ammonia levels; strong genotype-phenotype relationship



5 enzymes and 1 cofactor (NAGs) are critical for ammonia → urea conversion

Therapeutic goal: increase OTC gene product to reach >5% of normal

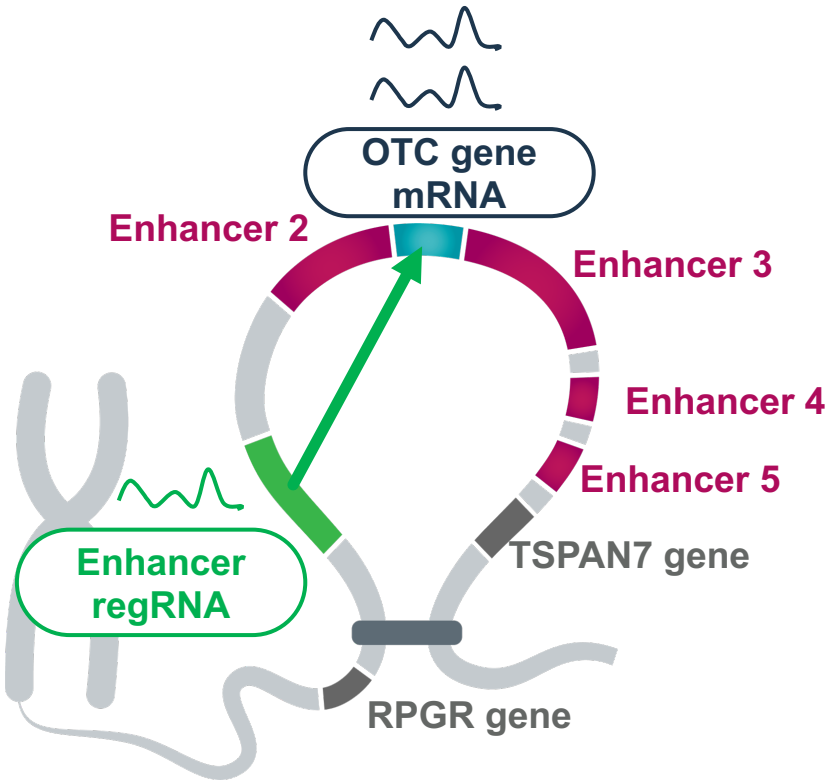
Individual OTC-deficient Patient Data[1]

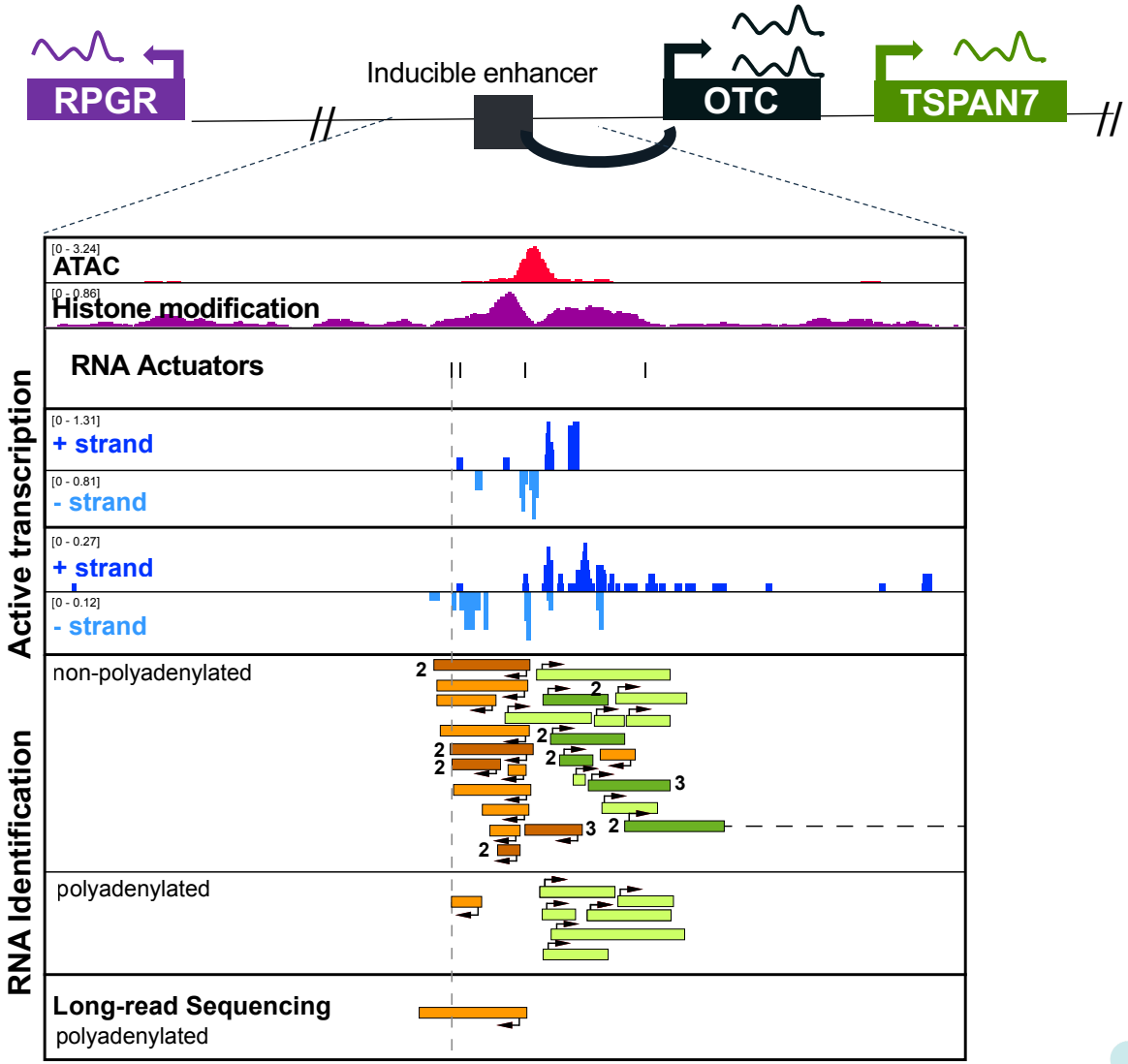


- OTC gene is located on *X* chromosome

1: Wakiya et al., Mol Gen Met, 2012 (105)-404

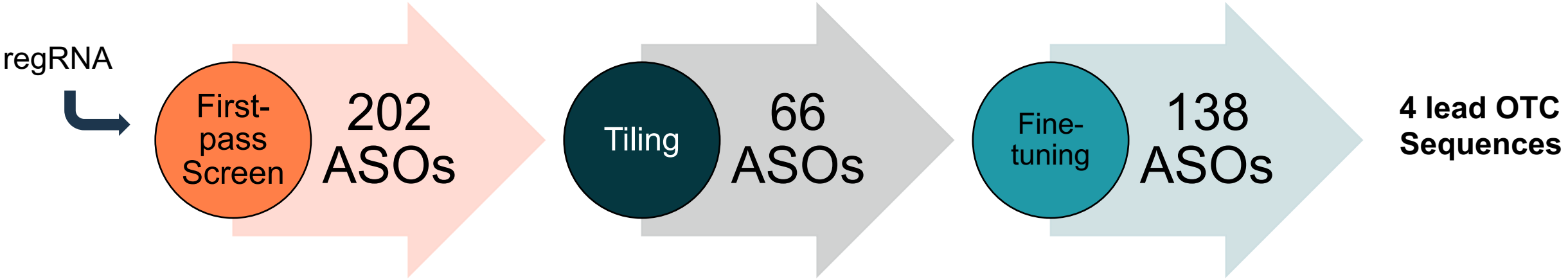
CAMP4 platform identified novel regRNA transcripts to upregulate *OTC* mRNA



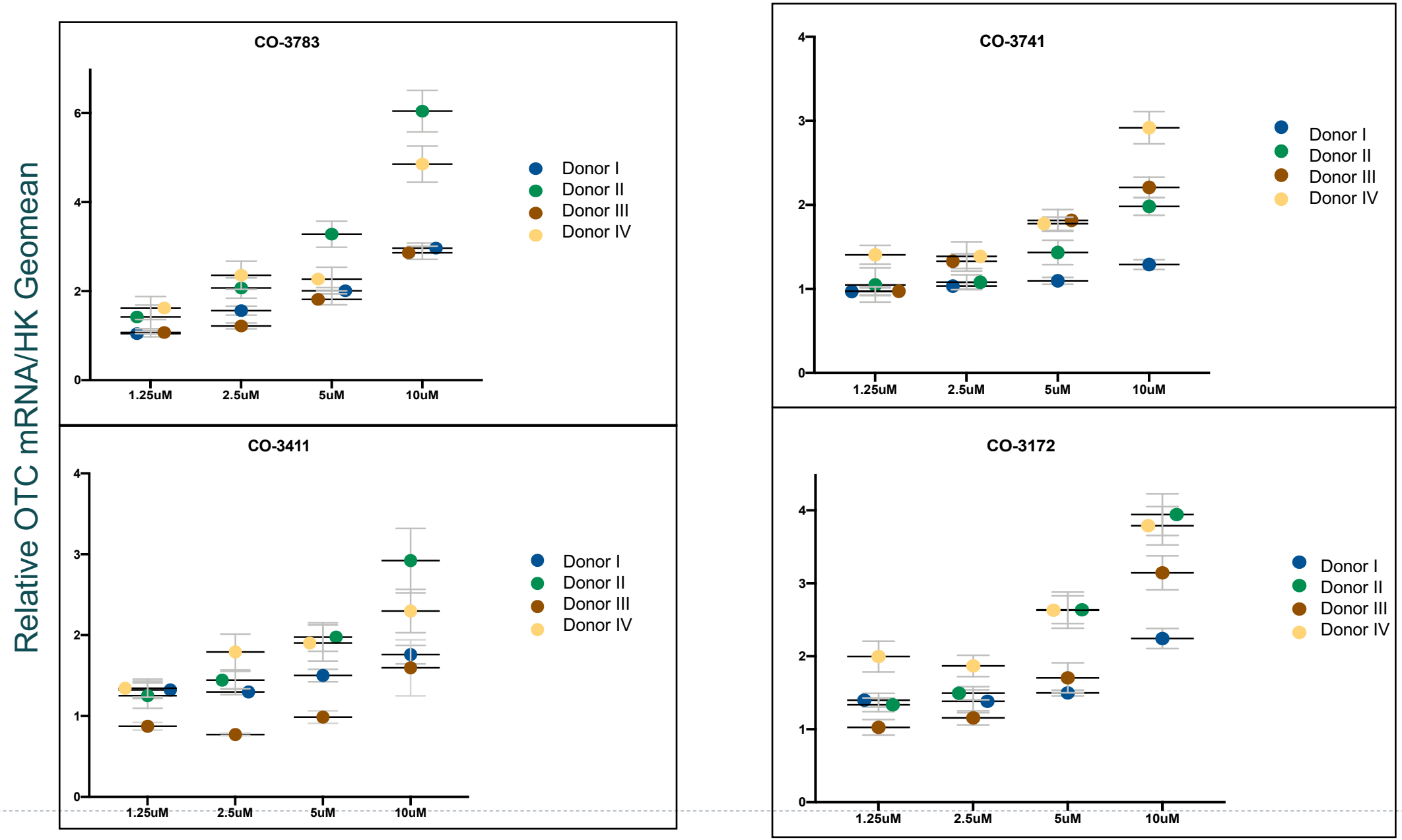


Overall process of RNA Actuator screening

Total 406 sequences were screened for targeting OTC regRNAs

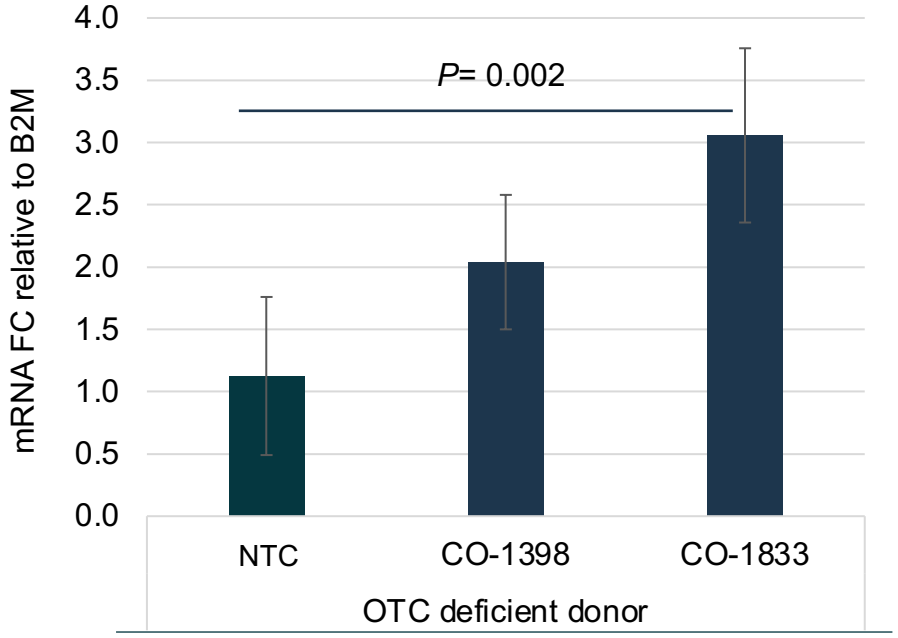


regRNA targeting RNA Actuators upregulate *OTC* mRNA dose-dependently



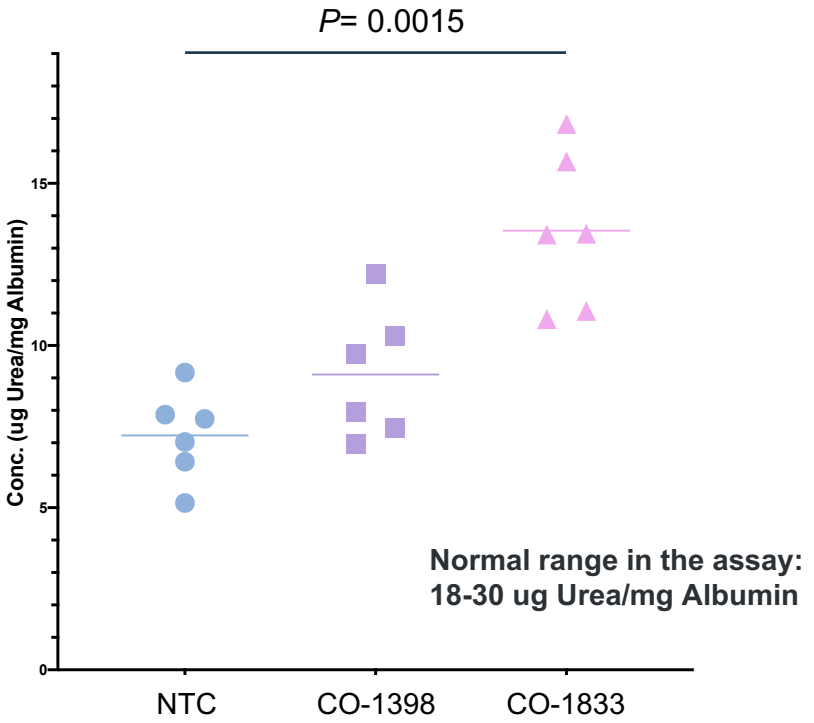
RNA actuators led to increased ureagenesis in patient cells[1]

OTC mRNA levels in response to treatment



- CO-1398, 1833: unique sequences targeting the regRNA

Ureagenesis read-out cultured cells



P values calculated by one-way ANOVA

- c.-106C>A (Allele ID 480410, late-onset OTC deficiency) - pathogenic (dbSNP: rs749748052), leading to decreased OTC mRNA[1].
- Variant associated with 10-25% of normal OTC activity

Developing a mouse surrogate for *Otc* mRNA

Identified regRNA for mouse *Otc*

- The human *OTC* enhancer is structurally conserved in mouse but the sequences are not conserved

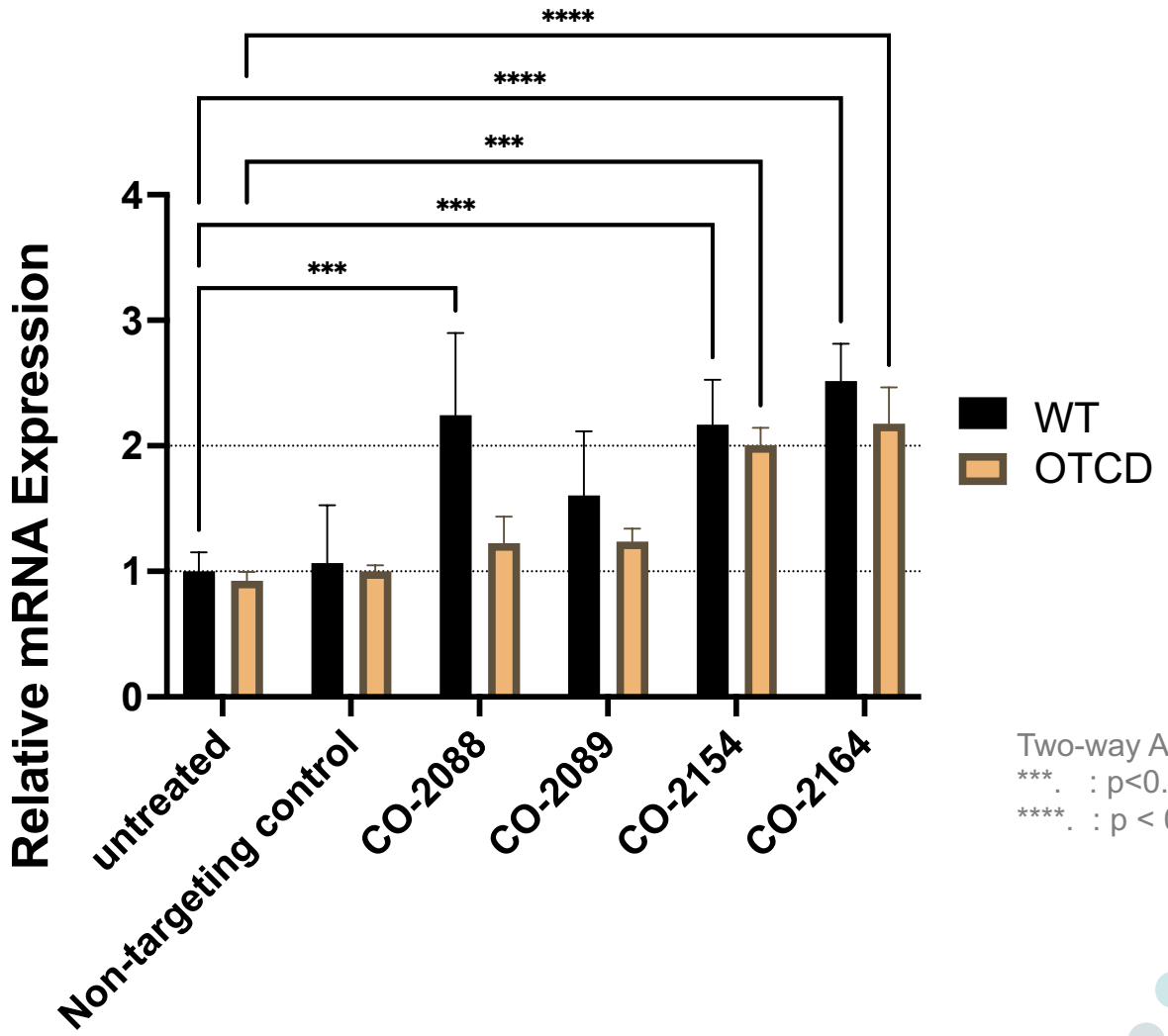
Designed and screened RNA actuators

- Screened for impact on *Otc* mRNA with RNA Actuators

Otc deficient (*Otc*$^{spf/ash}$) mouse model[1]

- The spf ^{ash} mouse has a variant c.386G>A, p.Arg129His in the *Otc* gene that impact splicing
- Otc mRNA levels are decreased (5~12% of wt control) in spf/ash livers
- Male spf ^{ash} mice have a mild biochemical phenotype with low OTC activity (5%-10% of wild-type)

RNA Actuators increase mouse *Otc* mRNA levels



Two-way ANOVA
***. : p<0.001
****. : p < 0.0001

1. Briand et al. 1982, Ohtake et al. 1987, Allergri et al. 2019, Rivera-Barahona et al. 2015

To summarize…

- Identified regRNA that controls OTC gene expression
- Identified regRNA targeting RNA actuators that can upregulate human *OTC* mRNA in a dose-dependent manner -> increase in ureagenesis
- RNA actuators targeting mouse regRNA increase Otc mRNA in both wildtype and Otc deficient cells
- This approach offers a novel way of treating a disease caused by a hypomorphic allele by upregulating the endogenous gene expression using RNA Actuators.
- Our results indicate that CAMP4's RAP™ technology may provide precise, potent therapeutics that can be programmed to treat thousands of diseases.

Upcoming

- Test lead human *OTC* regRNA targeting RNA Actuators for
  - With GalNAc to test for NHP pharmacology, safety study

- Test lead mouse *Otc* regRNA targeting RNA Actuators for
  - In Otc deficient mice for Proof of Concept (PoC) read-out