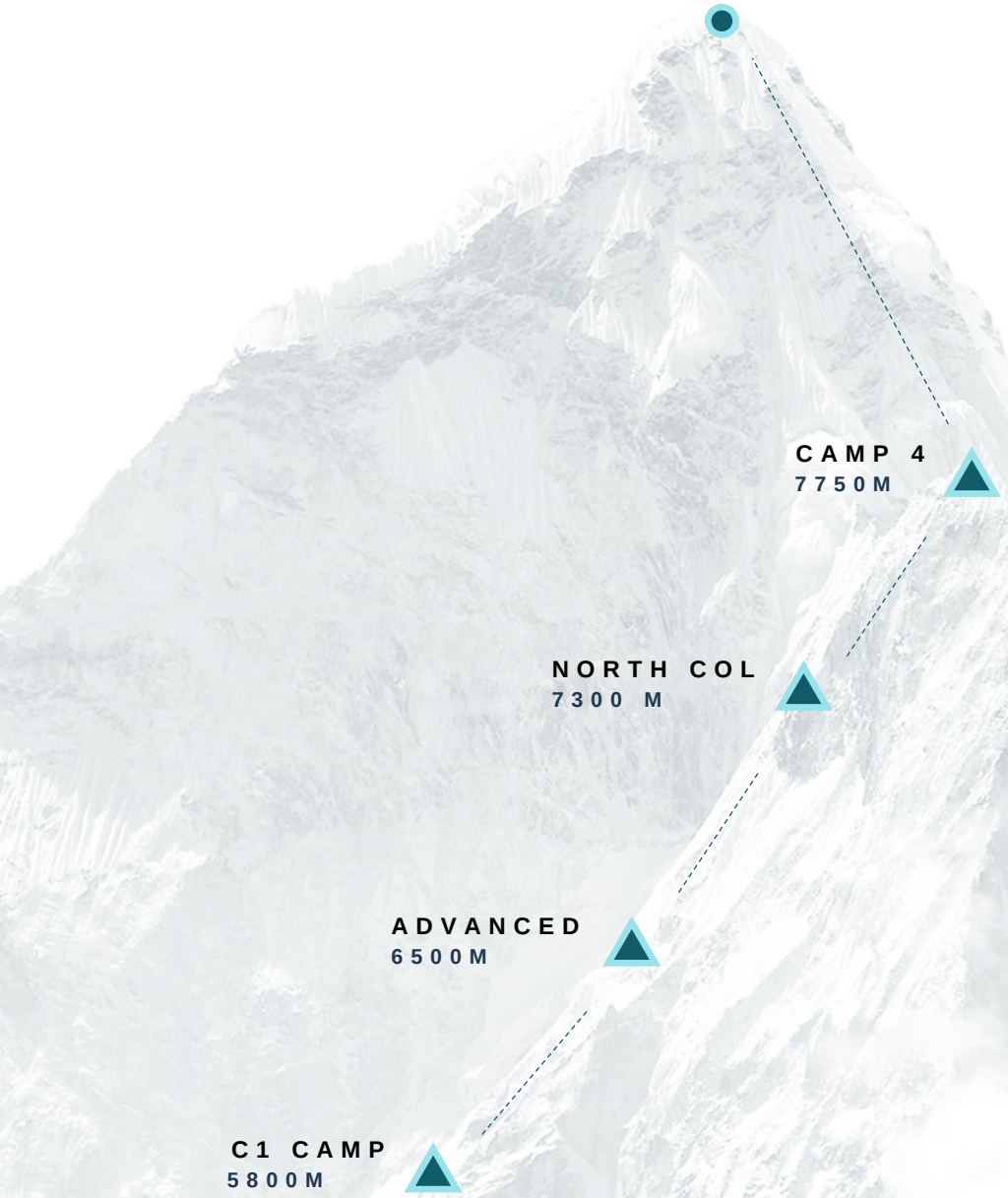

Targeting Regulatory RNAs with Antisense Oligonucleotides for the Potential Treatment of Urea Cycle Disorders

Dan Tardiff, SVP Head of Discovery

ASGCT Conference, May 16, 2025

Forward-Looking Statements

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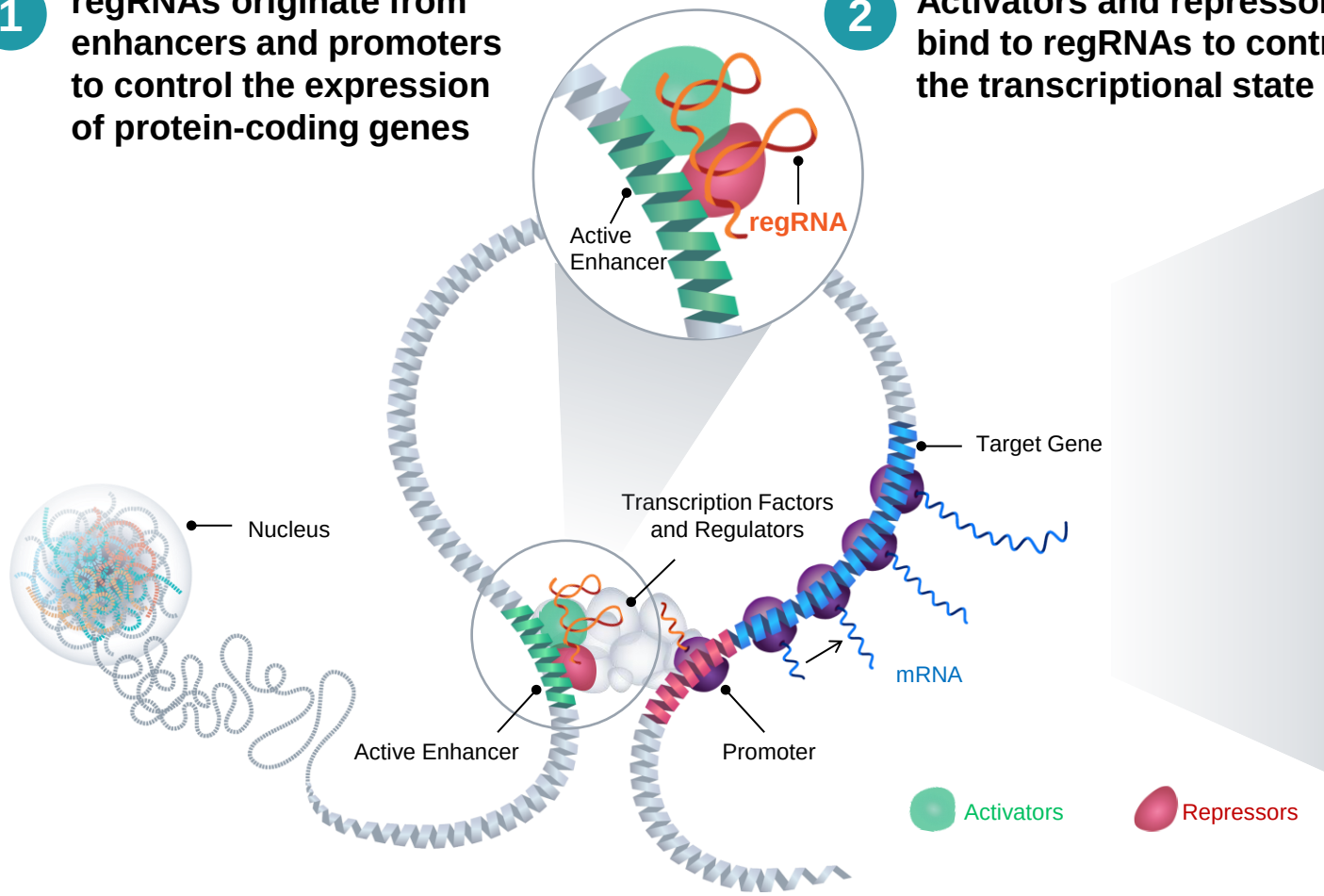
regRNAs play a central role in the regulation of every gene's expression

1 **regRNAs originate from enhancers and promoters to control the expression of protein-coding genes**

2 **Activators and repressors bind to regRNAs to control the transcriptional state**



- All actively transcribed genes also express regulatory RNAs
- regRNAs bind to and "tether" transcription factors to site of transcription to create high local concentration, or kinetic trap
- Activity proximal to their own synthesis ensures specific regulation of gene expression
- Expression is regulated within a physiological range

Source: Sharp et al. (2022) RNA 28: 52-57; Henninger et al. (2021) Cell 184:207-225; Sartorelli & Lauberth (2020) Nat. Struct. Mol. Biol. 27: 521-8; Oksuz et al. (2023) Molecular Cell 83: 2449-63.

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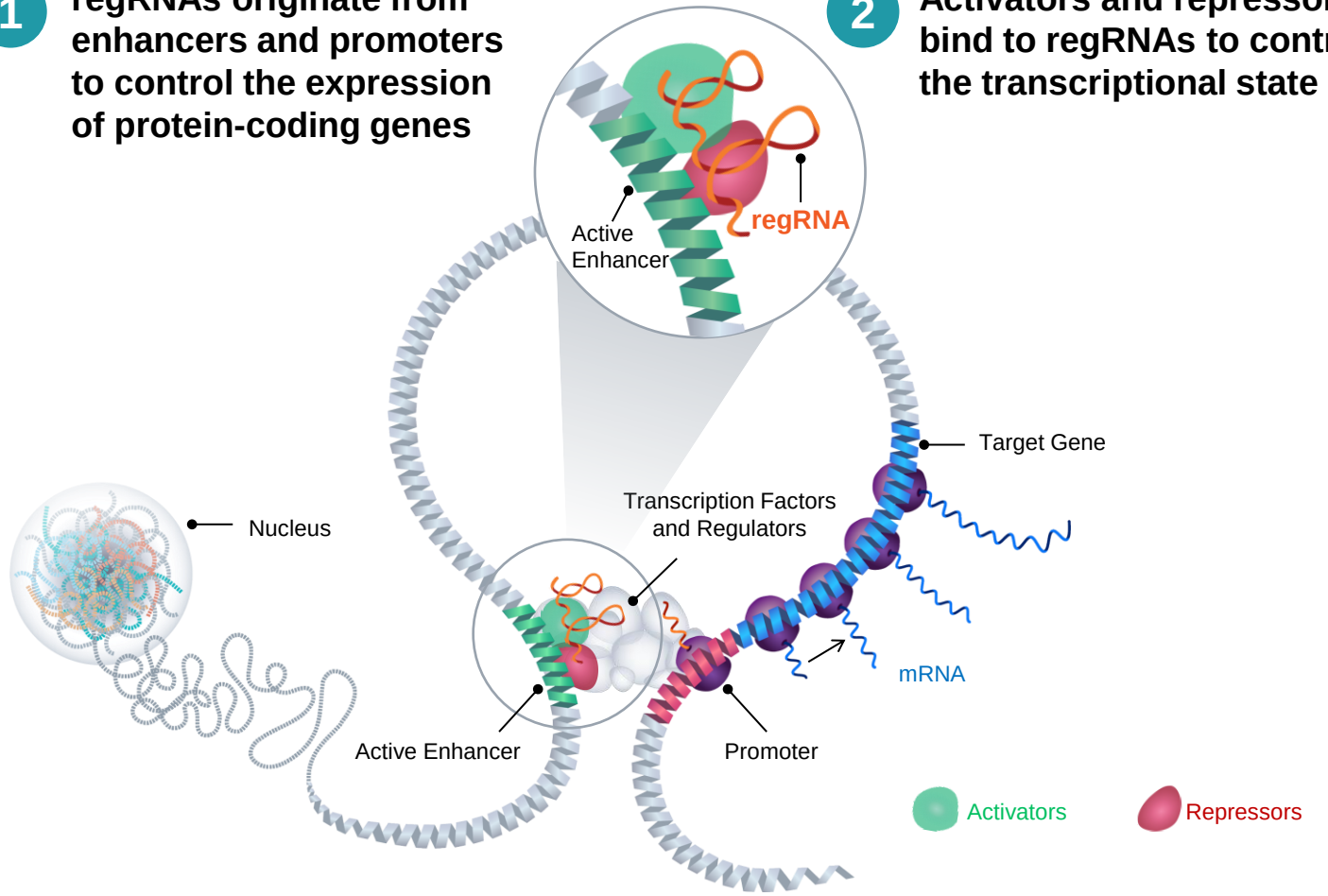
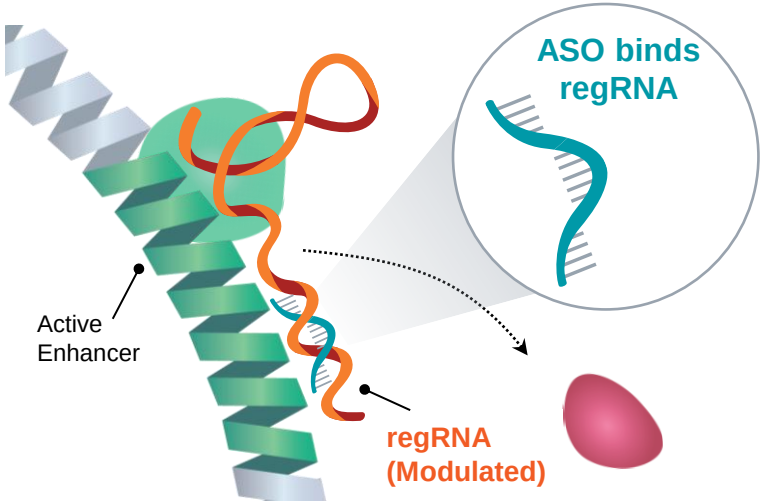


3 **ASOs disrupt the interactions between repressors and regRNAs enabling increases in gene expression**



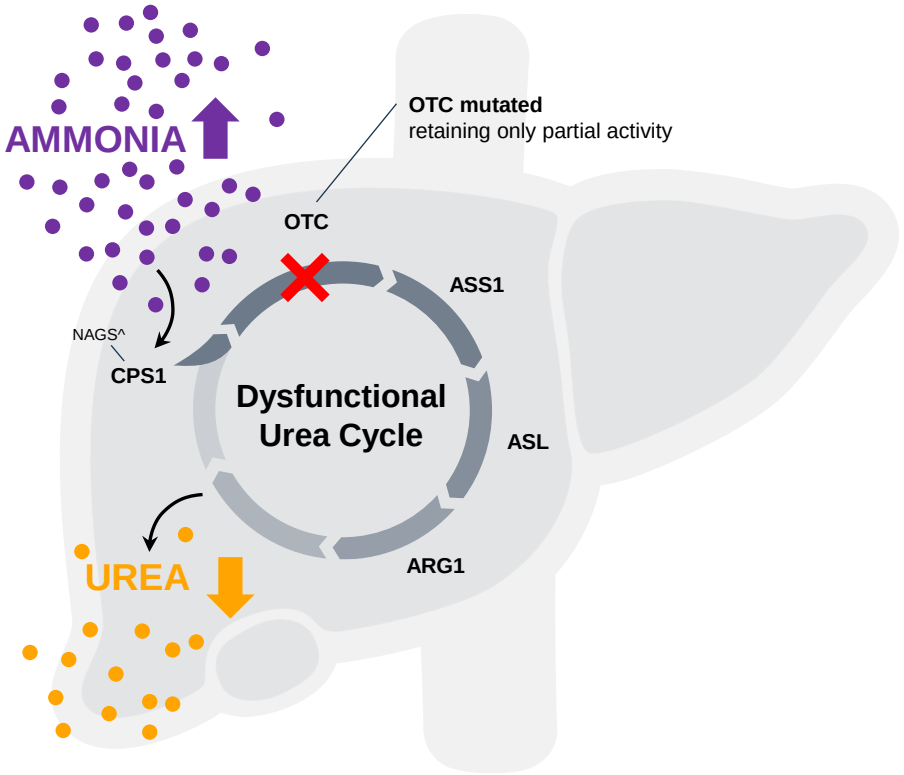
Increased mRNA expression

Addresses root cause of **haploinsufficient or partial loss-of-function diseases by** returning **targeted protein levels** to within a healthy range

Source: Sharp et al. (2022) RNA 28: 52-57; Henninger et al. (2021) Cell 184:207-225; Sartorelli & Lauberth (2020) Nat. Struct. Mol. Biol. 27: 521-8; Oksuz et al. (2023) Molecular Cell 83: 2449-63.

Urea Cycle Disorders (UCDs) are a set of life-threatening inherited metabolic diseases characterized by the accumulation of toxic ammonia

Mutation in one of several urea cycle enzymes or transporters causes suboptimal ureagenesis (conversion of ammonia to urea)



*Enzyme levels >5% of normal, severe symptoms persist beyond the first month of life
^NAGS enzyme produces the co-factor NAG which activates CPS1

UCD background

- Ammonia accumulates to dangerous levels without warning, posing a constant risk of life-threatening hyperammonemic crises and irreversible brain damage
- Collectively, we believe there are **~4,300** diagnosed symptomatic patients in the US; potential for opportunity to expand with increased diagnosis rates
  - CAMP4 UCD severe* opportunity is estimated to be 2,300 diagnosed symptomatic patients out of 3,700 prevalent
  - Female OTC Heterozygotes represent an estimated **incremental** 2,000 diagnosed symptomatic patients

Current standard of care is symptomatic

- No mutation agnostic disease modifying treatments available
- Symptomatic therapies include nitrogen scavengers (3-4 pills / day) and a strict diet that borders on malnutrition
- Constant risk of hyperammonemic crises which can be caused by infection, lapse in diet or medications

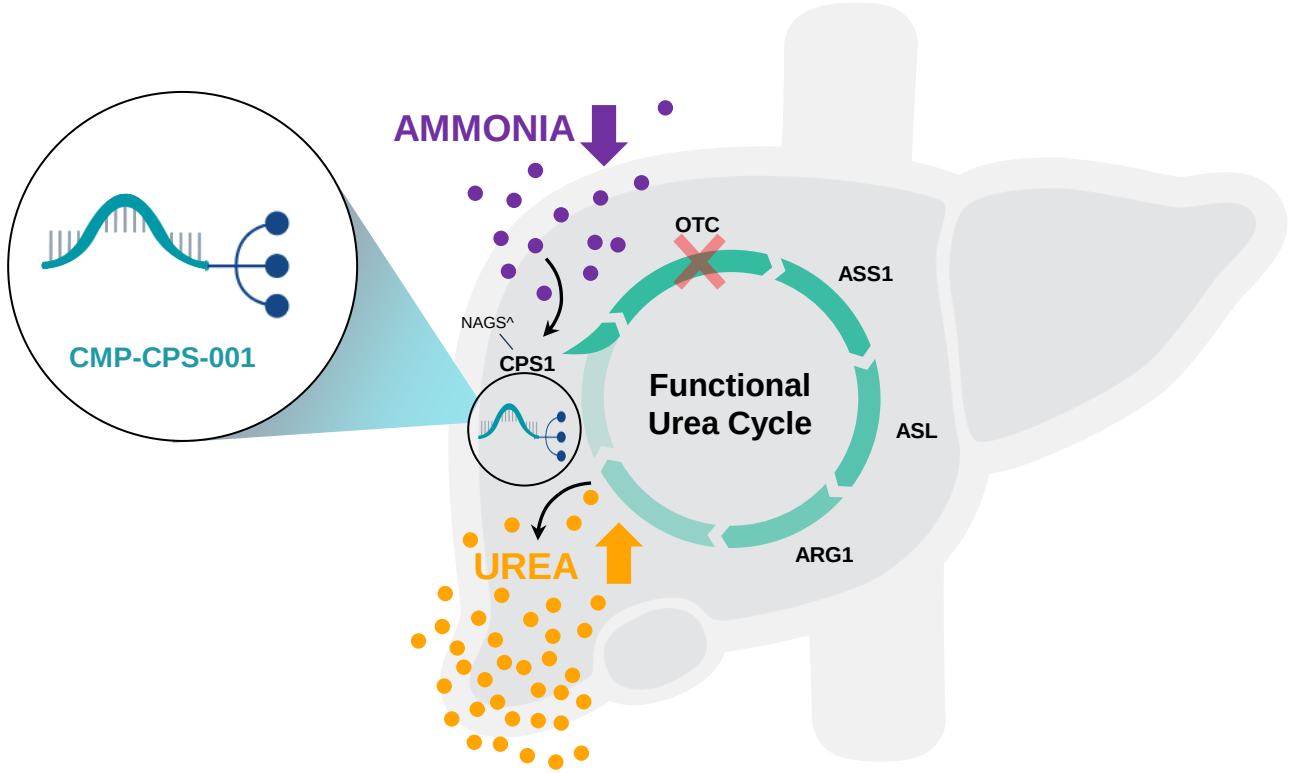
Sources: Yilmaz et al. (2022), Buerger et al. (2020), Posset et al. (2019), Sen et al. (2024), Batshaw et al. (1986), Trinity Primary Research – N=6 OTCd KOLs, April 2025, Komodo Claims Data 2016-2024

Trinity Life Sciences analysis of Komodo Claims data shows ~3.1K unique female OTC patients with at least 2 instances of ICD-10 code E72.4 diagnosis from 2016-2024

CAMP4 is targeting increased expression of CPS1, resulting in amplified ureagenesis and improved conversion of ammonia to urea

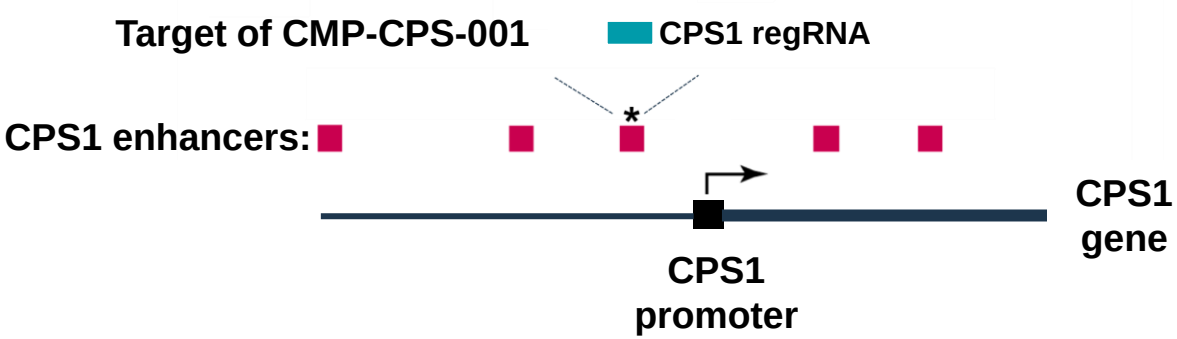
CPS1 is the gatekeeper of the urea cycle

CMP-CPS-001 is a GalNAc-conjugated ASO that binds to a CPS1-specific regRNA to increase CPS1 expression and upregulate the expression of multiple urea cycle enzymes to amplify the conversion of ammonia to urea, potentially addressing more than 90% of patients with late onset UCDs.

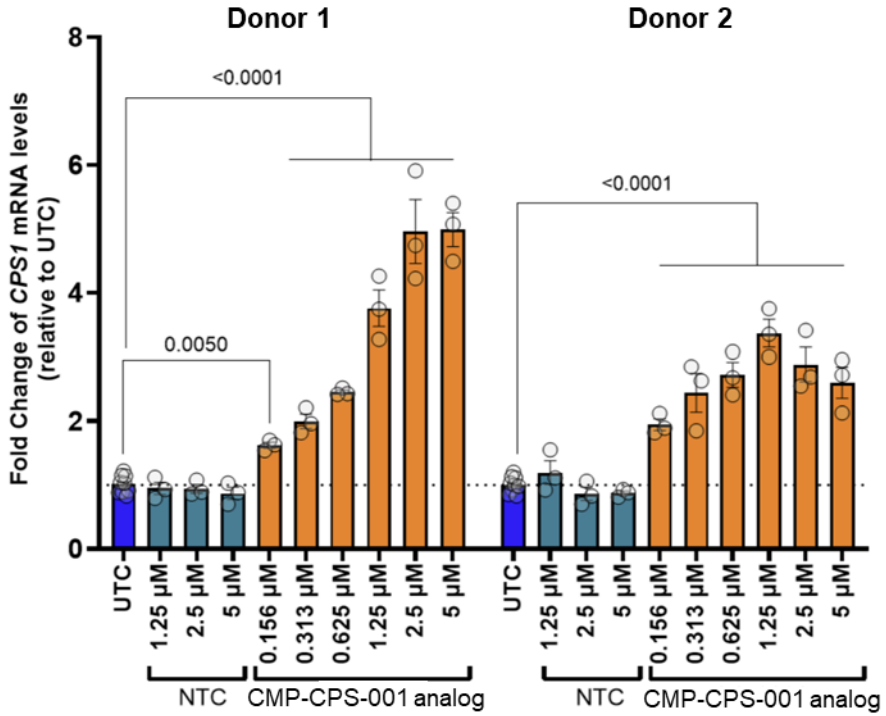


CMP-CPS-001 targets the key regRNA controlling CPS1 expression

Human *CPS1* regulatory regions



CMP-CPS-001 increases *CPS1* mRNA in primary WT hepatocytes



Activity confirmed in OTC deficient donor cells with CMP-CPS-001 analog (clinical candidate without GalNac)

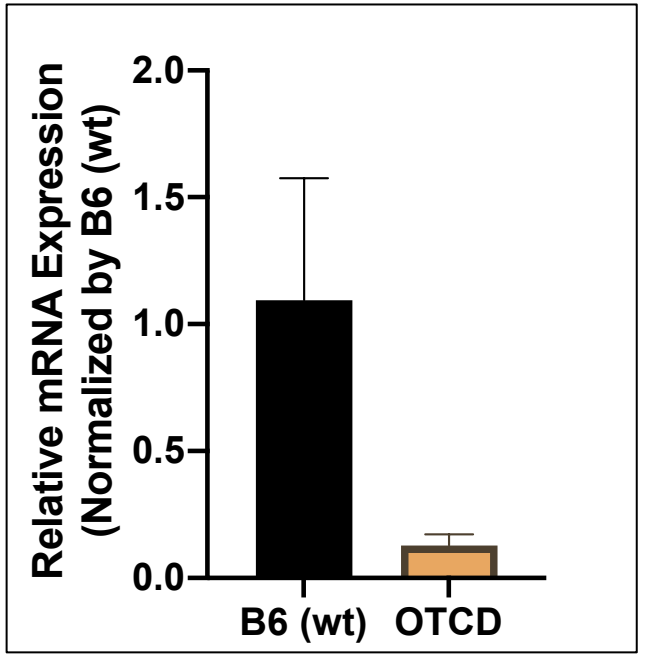
NTC = non-targeting control

A surrogate ASO targeting mouse *Cps1* regRNA reduces ammonia in an Otc-deficient mouse model

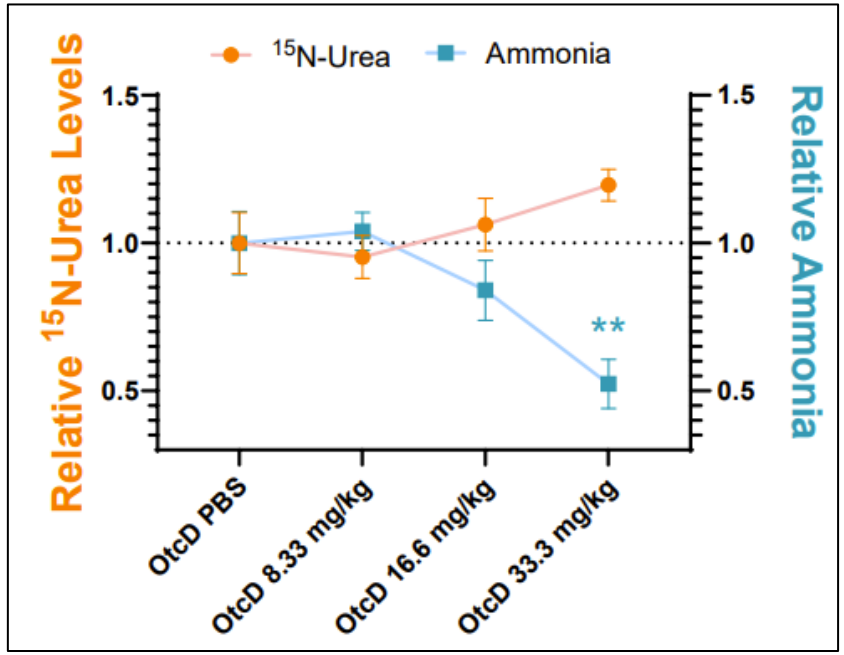
- The Otc$^{spf\text{-}ash}$ mouse model carries a patient mutation in Otc that reduces mRNA levels
- Otc activity is 5%-10% of wild-type[1]
- Model displays elevated ammonia relative to wild-type mice following an acute ammonia challenge

- ASO was shown to cause significant ~50% reduction in toxic ammonia (approx. WT levels)
- Correlated with ~20% increase in urea production

Otc-deficient mice have <10% of WT levels in Liver

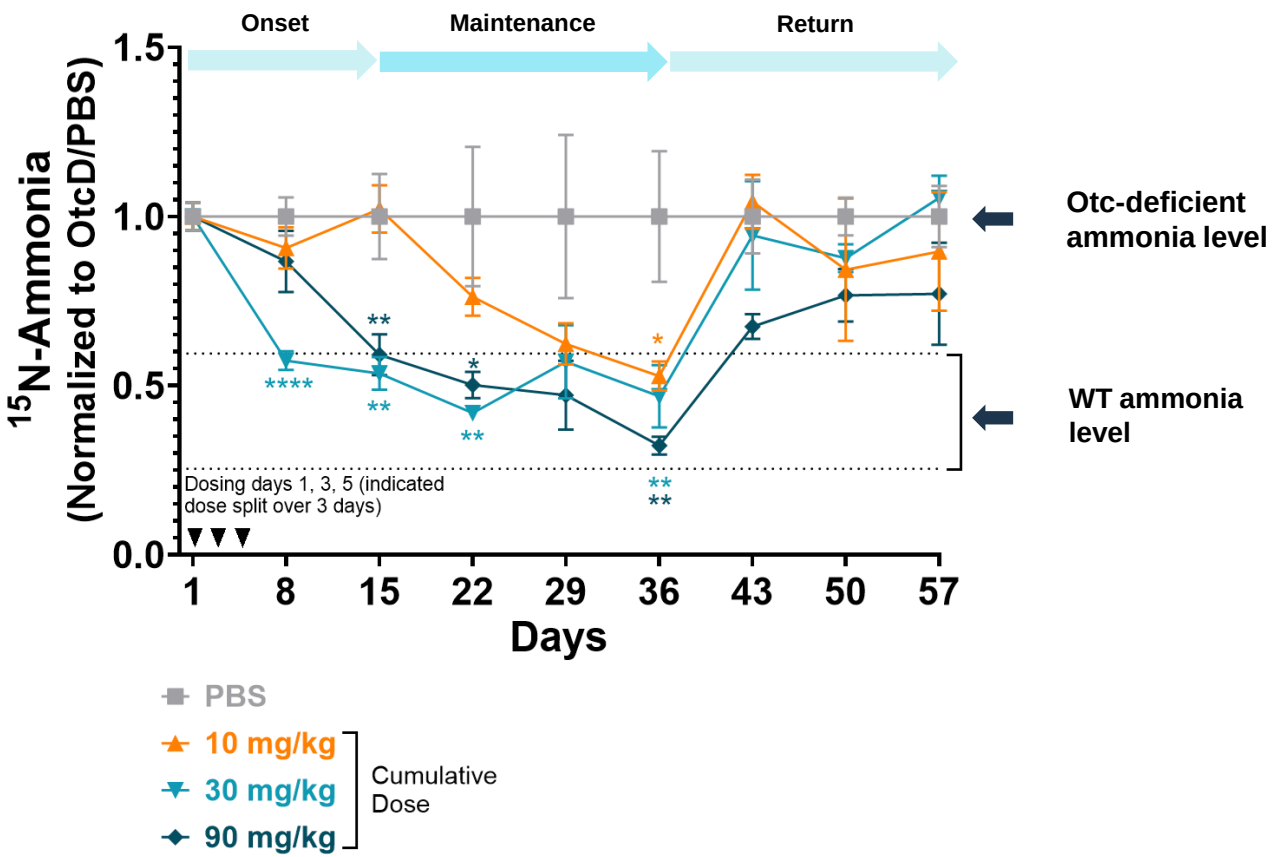


Ammonia levels decrease and urea increases with ASO treatment



[1]Hodges and Rosenberg, PNAS, 1989

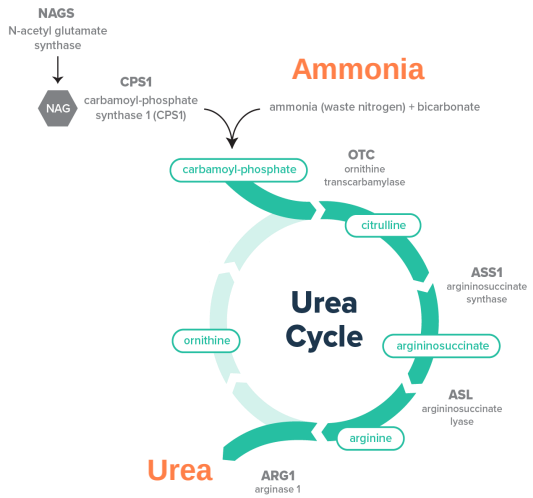
Surrgate ASO targeting mouse *Cps1* regRNA in Otc-deficient mice reduces ammonia and supports once-monthly dosing



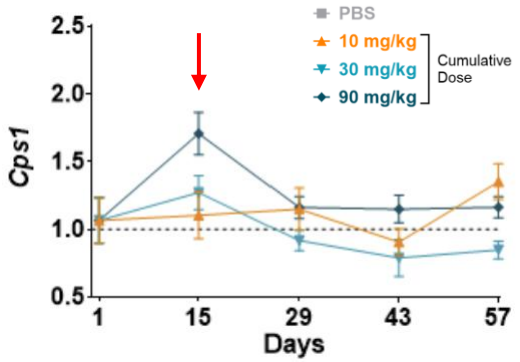
- Dose-dependent reduction in ammonia levels (corresponding increase in urea; data not shown)
- Maximal effect achieved in 2-3 weeks
- Response persisted for ~1 month
- Supportive of once-monthly dosing in the clinic

OtcD: Otc-deficient

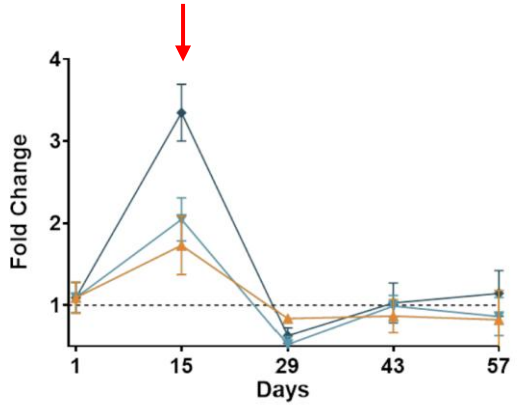
Dose & time-dependent increase in *Cps1* mRNA & regRNA, as well as multiple additional RNAs from other genes in urea cycle pathway



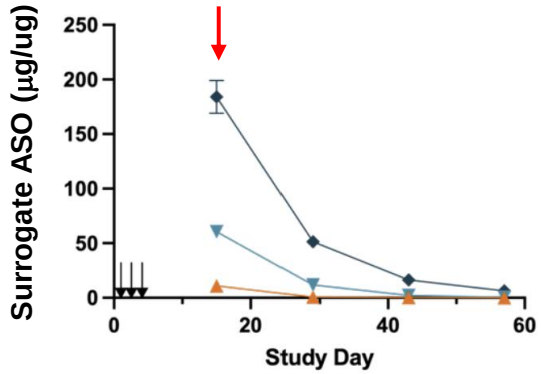
↑ mRNA at 2 wks



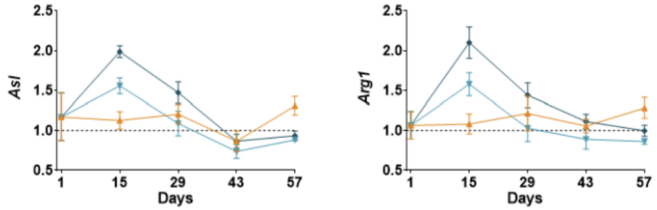
↑ regRNA at 2 wks



~12-day tissue half-life



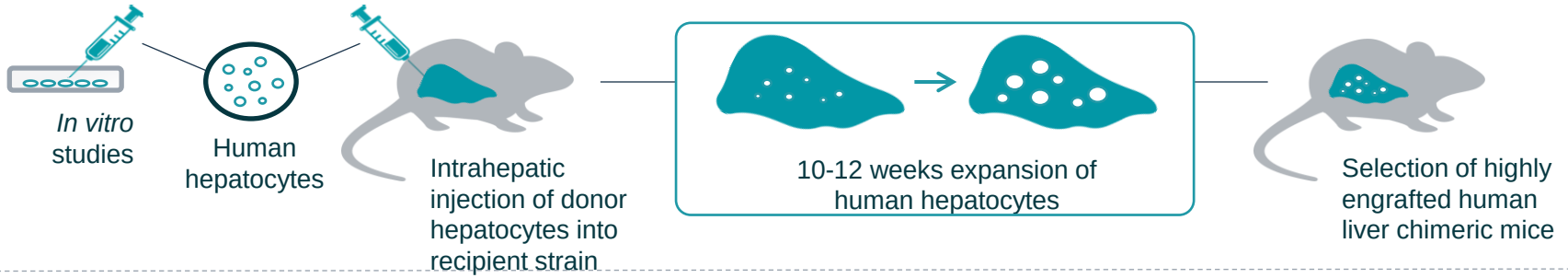
↑ *mRNA in additional urea cycle enzymes*



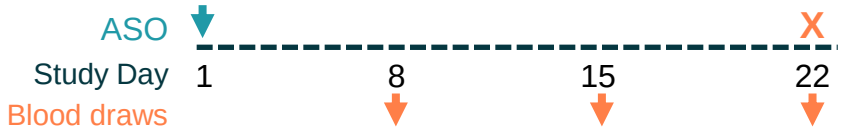
- ***Cps1*** **mRNA and regRNA peak at 2 weeks post-dose**
- **Additional urea cycle enzyme mRNAs increase with comparable kinetics**
- **ASO clearance coincides with decline in mRNA effects**

Treating wild-type humanized liver mice with ASO targeting *CPS1* regRNA reduces ammonia and increases urea levels

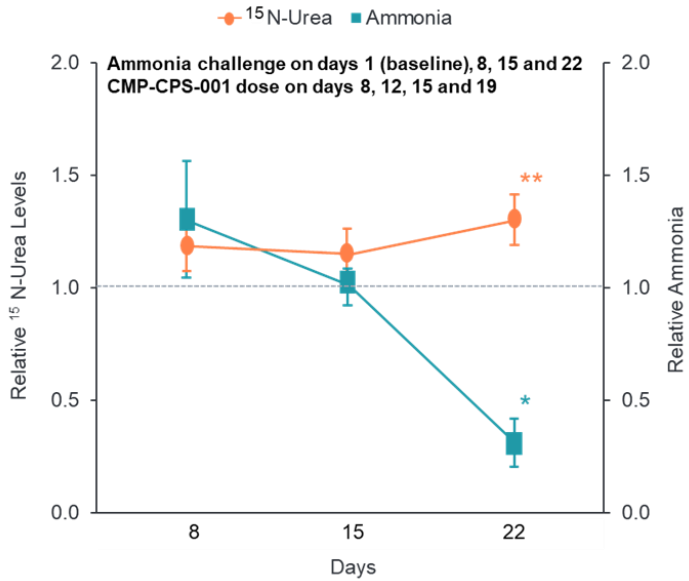
"Humanized" mice have livers repopulated with human hepatocytes



Study Design



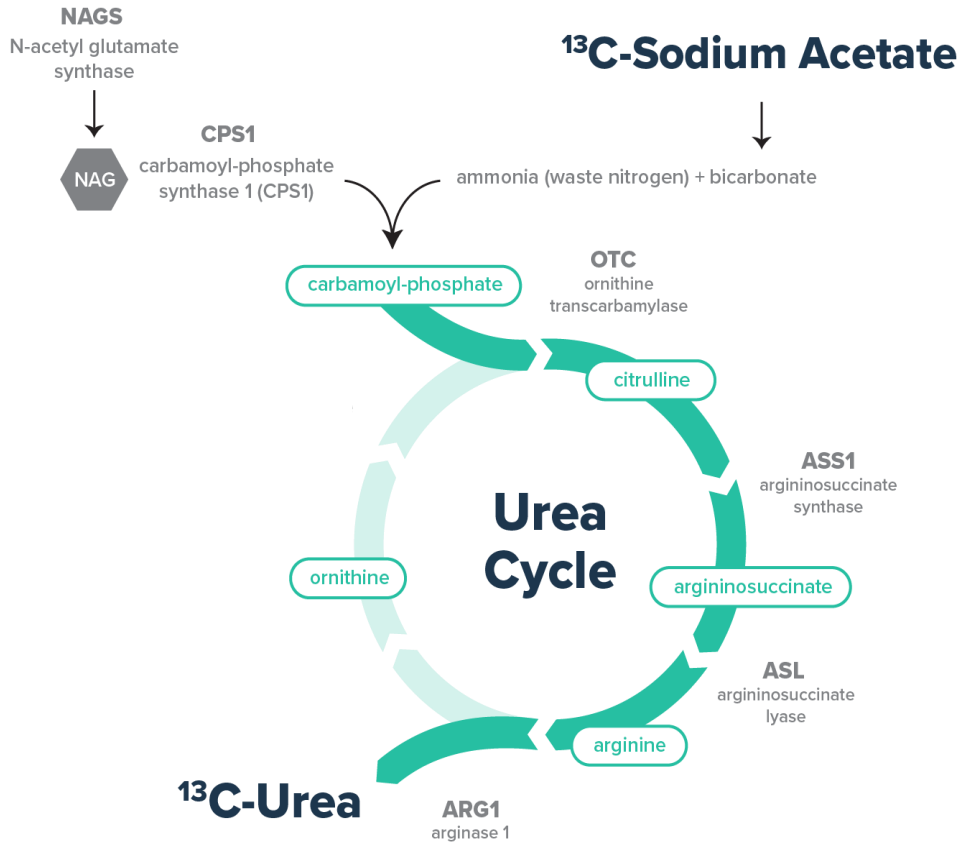
CMP-CPS-001: GalNAc-conjugated ASO designed for enhanced hepatocyte uptake properties



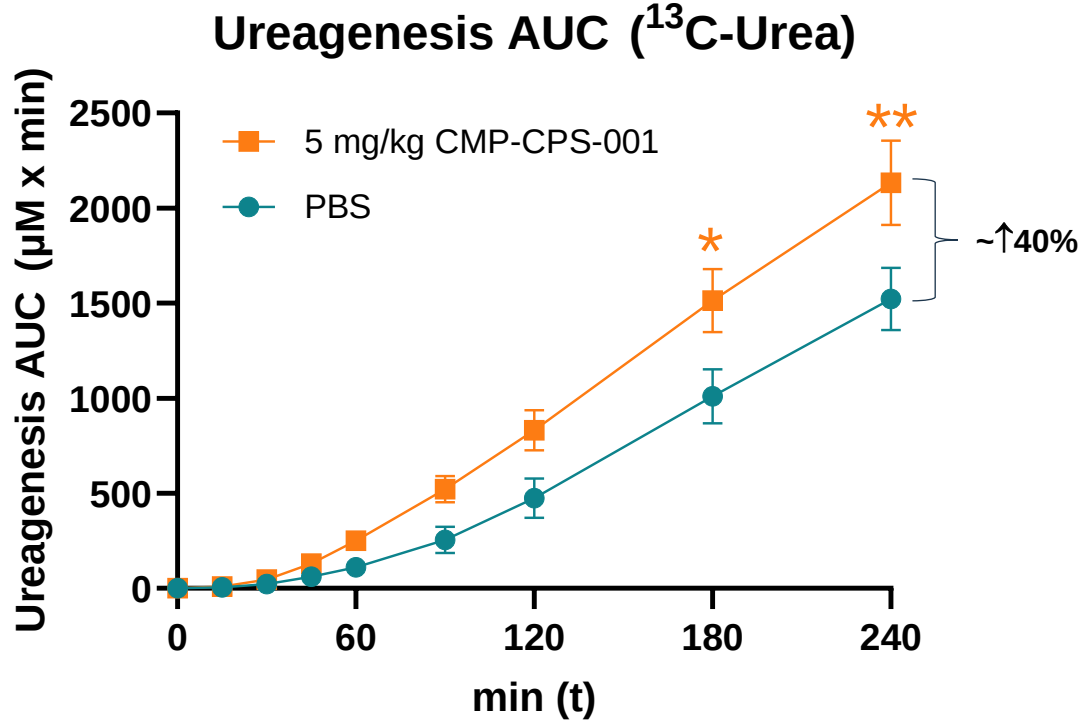
** denotes P<.01; * denotes P<.05

Using ureagenesis rate test (URT), CMP-CPS-001 was shown to increase ureagenesis up to 40% in wild-type cynomolgus monkeys

URT uses ^{13}C-labeled sodium acetate to measure ureagenesis



CMP-CPS-001 increases ureagenesis in NHPs



Error bars represent standard error of the mean; PBS denotes phosphate-buffered saline; * denotes p<.05; ** denotes p<.01.

Using ^{13}C-Sodium Acetate for ureagenesis in WT NHP
NHP administered drug once-monthly. Ureagenesis assessed up to 30 days after final dose. Data shown is one week after a second, final dose.

CMP-CPS-001 has the potential to be the first disease-modifying therapy for the treatment of the most prevalent UCDs by increasing ureagenesis

Preclinical proof of concept

Clinical candidate reduces toxic ammonia and increases ureagenesis

- **Human hepatocyte data:** Dose-dependent increase in CPS1 expression in normal and OTC deficient human cells
- **Otc-deficient mice data:** 20-30% ↑ ureagenesis compared to baseline, leading to ~50% ↓ ammonia (wild-type levels); ~1 month duration of action
- **Humanized mouse data:** 20-30% ↑ ureagenesis compared to baseline, leading to ~70% ↓ ammonia; ↑ CPS1 + downstream urea cycle enzymes
- **Non-human primate data:** ~40% ↑ ureagenesis

Phase 1 clinical design

Increases in ureagenesis in healthy volunteers could translate to improved ammonia clearance in UCD patients

- **Dosing:** Preclinical data supports once-monthly dosing
- **Biomarker:** Urea cycle activity (ureagenesis) can be monitored in healthy volunteers and patients using the ureagenesis rate test (URT)
- **Phase 1 study:** CAMP4 is utilizing URT in Phase 1 CMP-CPS-001 clinical study
- **Proof of concept:** Multiple companies have utilized the URT in healthy volunteers and in patients

Dr. Yuri Maricich: CMP-CPS-001 Phase 1 update, Abstract #334

Thank you to the entire CAMP4 Team, to our supporters, and especially to the patients and families who we seek to serve.