CHINOOK THERAPEUTICS

PO1620

Discovery of CHK-336: A First-in-Class, Liver-Targeted, Small Molecule Inhibitor of Lactate Dehydrogenase for the Treatment of Primary Hyperoxaluria

Jennifer H. Cox[1], Marc-Olivier Boily[1], Alex Caron[1], Amandine Chefson[1], Oliver Chong[1], Jim Ding[1], Valerie Dumais[1], Samuel Gaudreault[1], Robert Gomez[1], James Guthrie[1], Ross P. Holmes[2], Andrew J. King[1], John Knight[2], Jeff Lester[1], W. Todd Lowther[3], Renata Oballa[1], Michael D. Percival[1], Tao Sheng[1], Jayakumar Surendradoss[1], Joyce Wu[1], David A. Powell[1]

1. Chinook Therapeutics Inc., Vancouver, BC, Canada
2. University of Alabama at Birmingham, Birmingham, AL, United States
3. Wake Forest School of Medicine, Winston-Salem, NC, United States

©2020 Chinook Therapeutics. All Rights Reserved.

Primary Hyperoxaluria (PH)

Rare and severe disorder leading to oxalate overproduction and end stage renal disease (ESRD)

Genetic liver enzyme deficiency resulting in excessive oxalate production

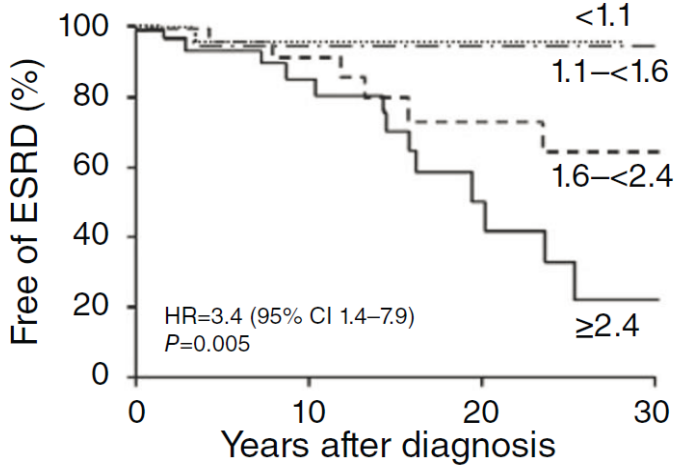
- Patients form many calcium oxalate kidney stones
- Median age of kidney failure in PH1 is 23 years
- Only curative treatment is dual kidney-liver transplant; no approved drug therapies

Lower urinary oxalate (UOx) levels associated with reduced risk of ESRD

Clinical proof of concept achieved by injectable siRNA agents (GO-siRNA for PH1 and LDHA-siRNA for PH1/PH2)

No oral, small molecule therapies with potential to treat patients with all types of PH have been reported

ESRD Risk by Urinary Oxalate Levels[1]



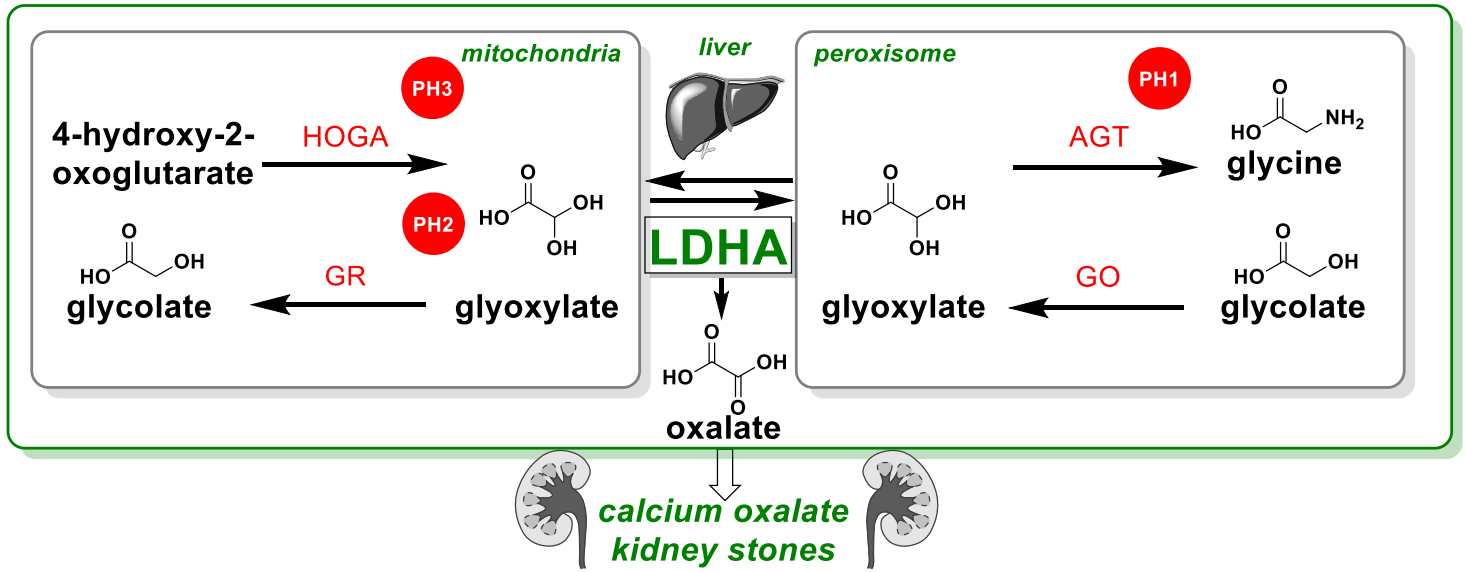
Disease Progression of PH

- Abnormal liver metabolism of glyoxylate produces **excess oxalate**
- Calcium **oxalate crystals form in the kidneys**
- Decline in kidney function results in systemic **oxalosis**
- Onset of **kidney failure**
- Dialysis awaiting **dual liver / kidney transplant**

1. Zhao et al CJASN 2016; 11(1): 119-126

CHINOOK THERAPEUTICS

Targeting LDHA Addresses All PH-Causing Mutations and Pathways



Three types of PH caused by different mutations:

- PH1: AGXT (AGT protein)
- PH2: GRHPR (GR protein)
- PH3: HOGA1 (HOGA protein)

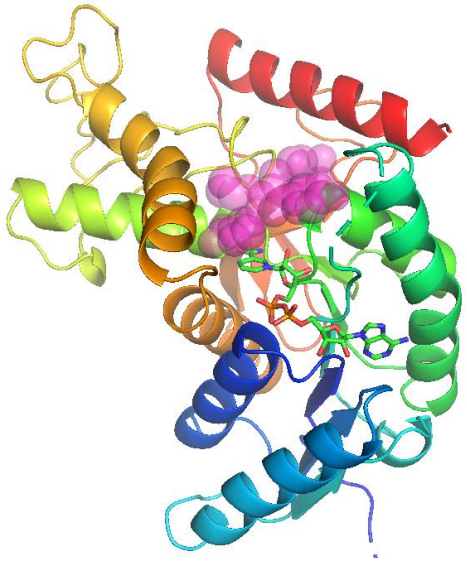
Lactate dehydrogenase (LDHA) is the final and committed step in production of oxalate from glyoxylate in the liver

- Represents a potential therapeutic target for all forms of PH, as well as other disorders arising from oxalate overproduction
- Complete loss-of-function of LDHA in humans results in exercise-induced muscle symptoms[1], therefore liver-targeting with low systemic levels is needed
- Liver-specific LDHA inhibition is expected to be safe and well tolerated

Chinook designed, synthesized and characterized hundreds of LDHA inhibitors with the goal of identifying a potent and selective compound with a liver-targeted tissue distribution profile for the treatment of all types of PH

1. Kanno et al Clinica Chimica Acta 1980; 108: 267-276

CHK-336 is a Potent LDHA Inhibitor in Enzyme and Hepatocyte Assays Across Multiple Species



Compound design and sub-nM potency guided by structural biology and X-ray crystallography of LDHA-inhibitor complexes

	ASSAY	CHK-336 IC_{50}
Enzyme	Human LDHA	**0.4 nM**
	Mouse LDHA	**0.1 nM**
Hepatocyte	Mouse Fresh Hepatocytes	**52 nM**
	Mouse Cryopreserved Hepatocytes	**80 nM**
	Rat Cryopreserved Hepatocytes	**130 nM**
	Monkey Cryopreserved Hepatocytes	**130 nM**
	Human Cryopreserved Hepatocytes	**131 nM**
PH1 Cell	Mouse *Agxt* Knockdown Hepatocytes (Oxalate Production)	**293 nM**

CHK-336 demonstrates potent inhibition of LDHA in enzyme assays (IC_{50} = 0.1-0.4 nM) and primary hepatocyte assays across multiple species (IC_{50} = 52-293 nM)

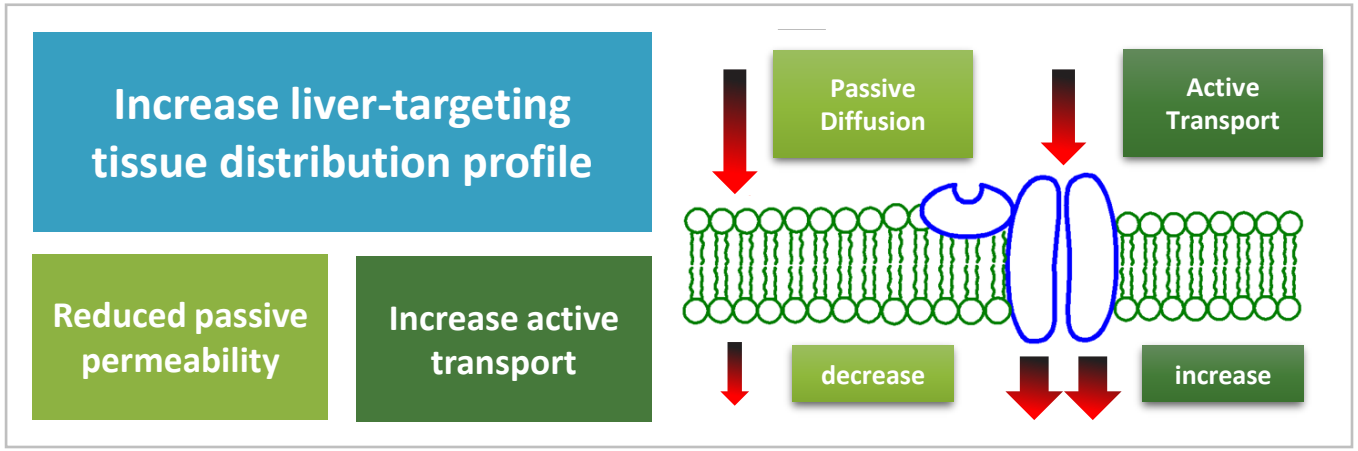
CHK-336 also demonstrated tight LDHA binding with a very slow off-rate (hours-days)

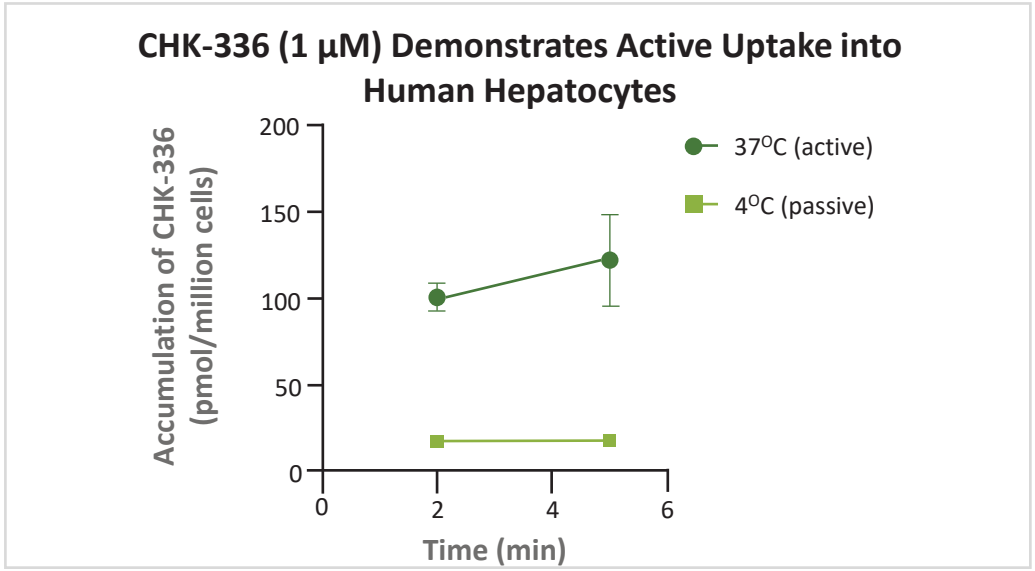
Design of a Liver-Targeted LDHA Inhibitor

- In order to reduce the potential for any muscle-related toxicities, as is observed with complete loss-of-function of LDHA, the Chinook team engineered a liver-targeted tissue distribution profile

- Strategy involves incorporating moieties that are recognized by liver-selective uptake transporters and reducing non-specific passive permeability

- CHK-336 demonstrates active uptake into human, monkey and rat hepatocytes

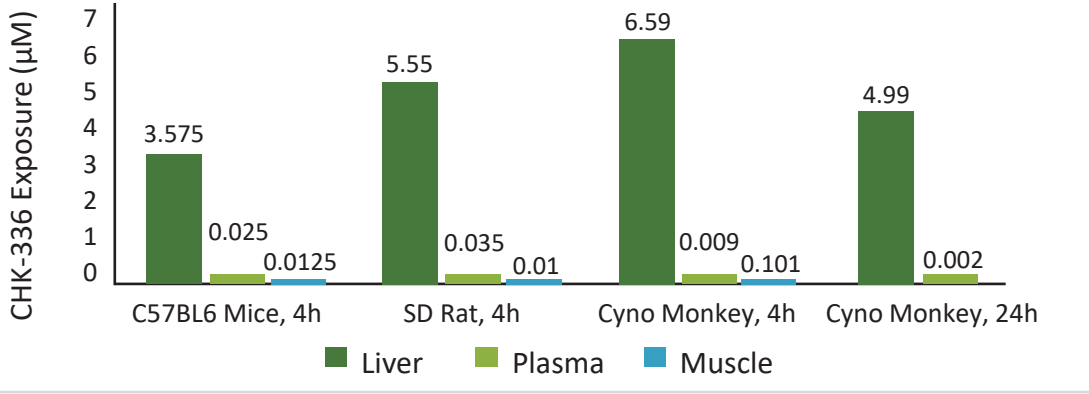


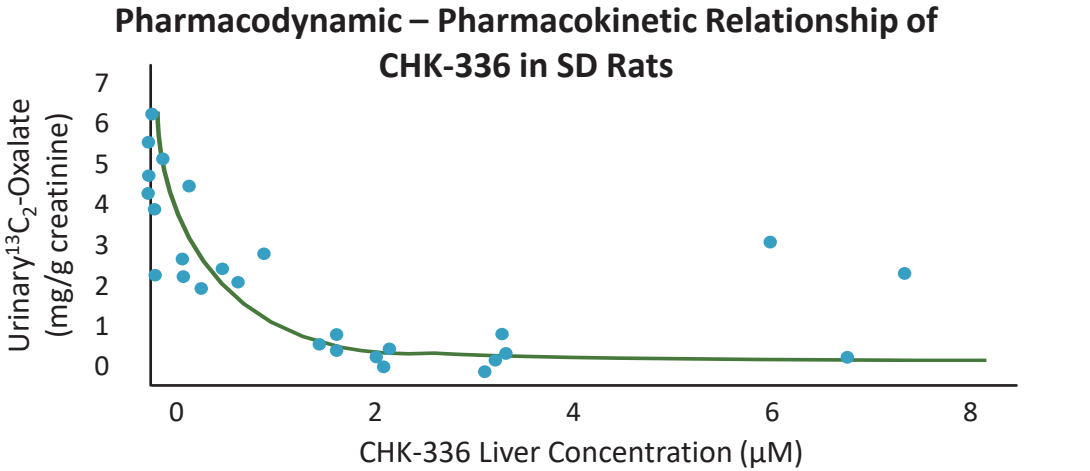


CHINOOK THERAPEUTICS

Pharmacokinetic and Pharmacodynamic Properties of CHK-336

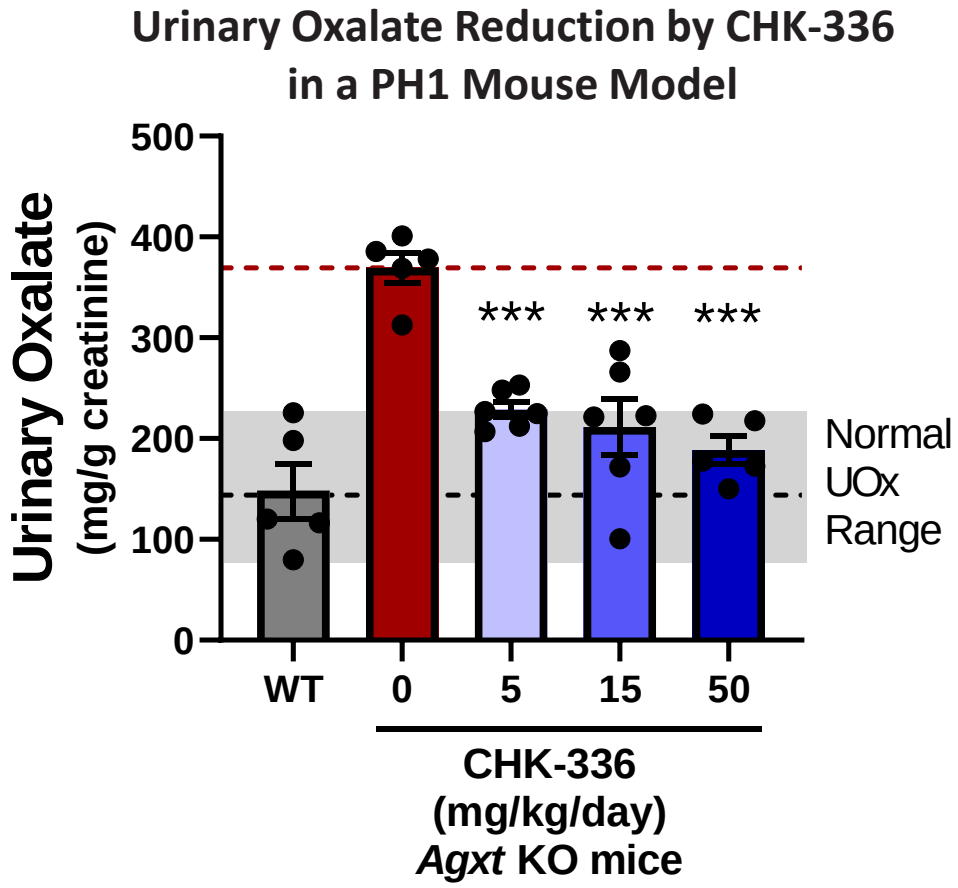
- CHK-336 exhibits a liver-targeted tissue distribution profile in mice, rats and monkey with high liver concentrations and low extra-hepatic tissue exposures
- Long liver half-life observed across species; driven by good metabolic stability and tight, slow-off rate binding of CHK-336 to LDHA in the liver
- Well-profiled pharmacodynamic effect in mice and rats driven by liver concentrations: liver EC_{50} of ≈3 µM
- Human PK predictions suggest CHK-336 has the potential to be a low, once-daily oral dose in humans





CHINOOK THERAPEUTICS

CHK-336 Produced Significant and Dose-dependent Reductions in Urinary Oxalate in a PH1 Mouse Model



- A mouse model of PH1 was generated by CRISPR-Cas9 deletion of exons 3-8 of *Agxt*; these mice exhibited elevated urinary oxalate as expected
- CHK-336 was dosed orally, once-daily for 7 days in male *Agxt* KO mice and urinary oxalate concentrations were compared to a vehicle control group
- **Low, oral, once-daily doses of CHK-336 significantly reduced urinary oxalate; majority of treated mice reached the normal range observed in wild-type mice**
- Analysis of liver concentrations of CHK-336 resulted in a PK/PD relationship with a liver EC_{50} of 1 – 5 μM CHK-336, consistent with rat liver PD values
- Similar data generated in a mouse *Agxt* knockdown model of PH1

Non-Clinical Safety Assessment Supports Continued Advancement of CHK-336 into IND-enabling Studies

Excellent in vitro Safety Profile

- Low risk of hERG mediated QT prolongation (IC_{50} > 30 µM)
- Non-mutagenic (negative in 5-strain AMES up to 5000 µg/well)
- Excellent off-target selectivity profile (<50% inhibition at 10 µM for 86 target panel, >450-fold selectivity for LDHA)

Low Drug-Drug Interaction (DDI) Potential

- Low risk of CYP-mediated DDI
  - No CYP3A4 inhibition or time-dependent inhibition (IC_{50} > 30 µM)
  - No CYP3A4 induction in hepatocytes (IC_{50} > 10 µM)

Promising Non-GLP in vivo Safety Profile

- Non-GLP in vivo safety studies suggest wide therapeutic margins over anticipated efficacious exposures
- Doses up to 1000 mg/kg/day explored in 14-day rat study

Conclusions

- Targeting LDHA, the terminal step in hepatic oxalate synthesis, represents a potential therapeutic strategy for all forms of PH, as well as other disorders arising from oxalate overproduction
- By potently blocking LDHA and engineering a liver-targeted tissue distribution profile, CHK-336 represents a potentially safe and effective oral small molecule for the treatment of primary hyperoxaluria
- CHK-336 shows robust efficacy in a PH1 mouse model at low, once-daily oral doses including the ability to reduce elevated urinary oxalate levels to the normal range
- The non-clinical safety assessment of CHK-336 conducted to date supports continued advancement into IND-enabling studies

CHK-336 is a first-in-class oral LDHA inhibitor with the potential to treat all subtypes of primary hyperoxaluria as well as other disorders arising from oxalate overproduction