A New Role for SLC6A19 Inhibition: Reducing Uptake of Nephrotoxins to Limit Kidney Injury

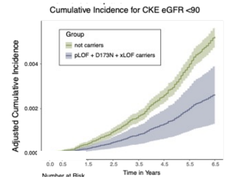
Robert R. Graham, Victoria A. Assimon, Jessica Wahlers, Hannah N. De Jong, Darian Ta, Lisa Pang, Brant Webster, Andrew H. Chang, Perryn C. Wong, Sarah M. Bronner, Yannan Xi, Karol Estrada, Maarten Hoek, Julie C. Ullman

Maze Therapeutics, South San Francisco, CA

Background

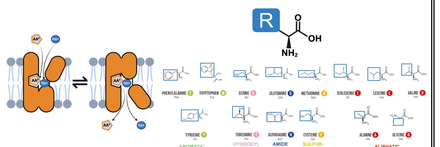
SLC6A19 (B^0AT1)

Loss Of Function Associated With Nephroprotection In Humans



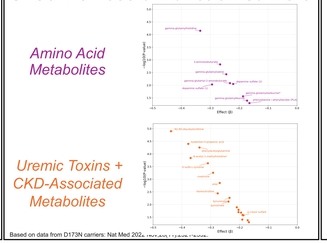
Cumulative incidence of the Combined Kidney Endpoint (CKE) over 6.5 years in carriers of SLC6A19 LoF variants (combined pLOF, D173N, and xLOF carriers) relative to non-carriers in matched UKB participants.

SLC6A19 Transports A Structurally Diverse Set Of Neutral Amino Acids



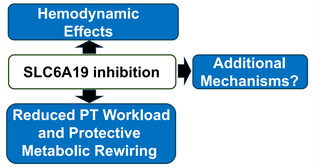
Sodium (Na^+) dependent neutral amino acid (AA^0) transporter that reabsorbs nutrients from the diet and filtered blood

Plasma Metabolites Altered in SLC6A19 Loss of Function Carriers

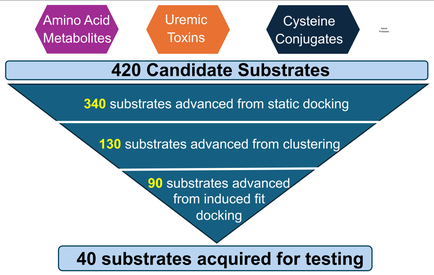


Based on data from D173N carriers: Nat Med 202...

Proposed Nephroprotective Mechanisms of SLC6A19 Inhibition

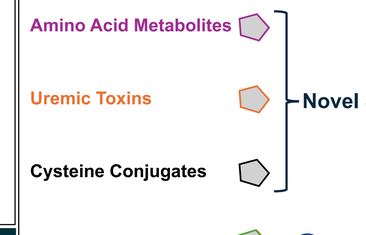


Study Design



Summary

SLC6A19 Substrates



Wider range of substrates than previously appreciated

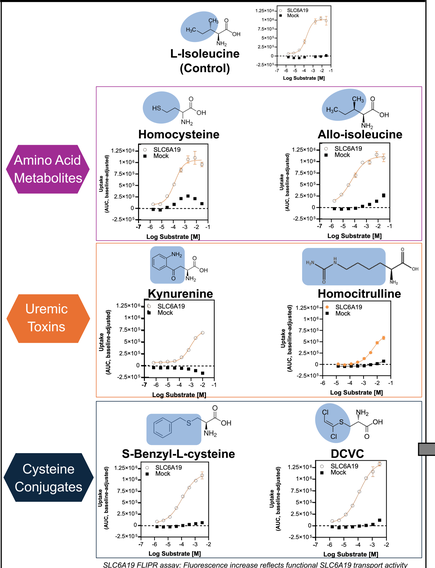
Novel substrates include nephrotoxins

SLC6A19 inhibition may protect the kidney by preventing the transport of nephrotoxic substrates into PT cells

An investigational small molecule inhibitor of SLC6A19, MZE782, is currently being evaluated as a potential therapy for CKD and Phenylketonuria (PKU).

Results

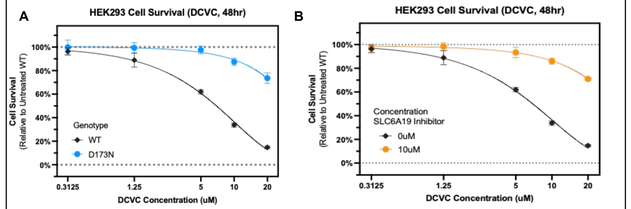
Novel SLC6A19 Substrates



SLC6A19 FLIPR assay: Fluorescence increase reflects functional SLC6A19 transport activity

Representatives of each class shown, 10 novel substrates total

SLC6A19 Inhibition Protects Kidney Cells From DCVC-mediated Toxicity *In Vitro*



D173N = SLC6A19 loss-of-function variant associated with improved kidney function and reduced disease progression

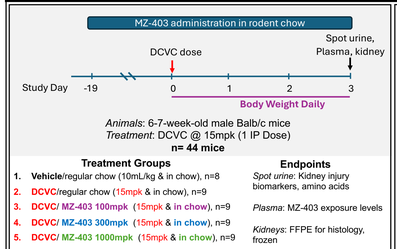
SLC6A19 inhibitor MZ-404 protects against DCVC toxicity similar to SLC6A19 loss-of-function.

HEK293 cells overexpressing CLTRN and SLC6A19 were treated with DCVC for 48H, and then cell viability was quantified using CellTiter Glo 2.0 (Promega). For all plots, survival = viability readouts normalized to untreated WT SLC6A19 controls, error bars show mean+/-SD, n=3, and curves show data fit to a 4-parameter logistic regression.

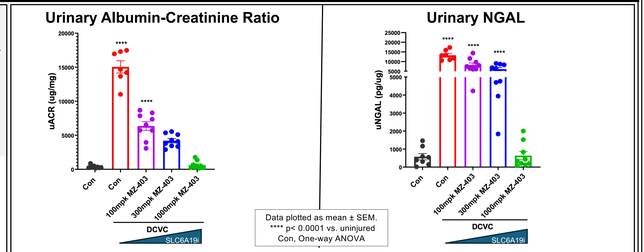
DCVC: A Pollutant Derived Cysteine Conjugate

TCE Trichloroethylene		DCVC (S-1,2-Dichloro-Vinyl)-L-Cysteine
• A historically high-use industrial solvent • TCE is a persistent groundwater contaminant	TCE + Glutathione → DCVC	• Known Nephrotoxin • DCVC is metabolized by β-lyases in PT cells to form a highly reactive and toxic thioketene

SLC6A19 Inhibition Protects Kidney Cells From DCVC-mediated Toxicity *In Vivo*

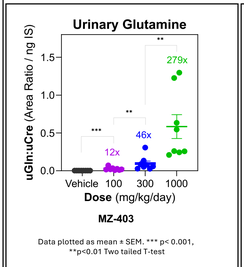


Overview of Study Design of SLC6A19i in the DCVC Nephrotoxicity Model



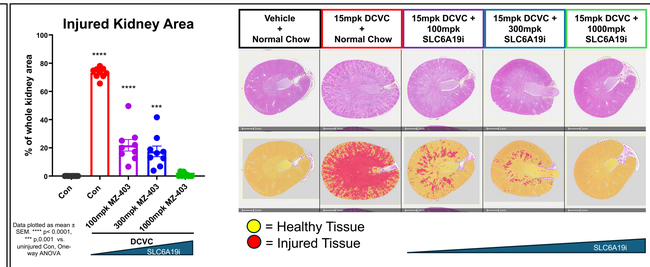
Data plotted as mean ± SEM. **** p< 0.0001 vs. uninjured Con, One-way ANOVA

SLC6A19i Dose Dependent Reduction of Kidney Injury Markers in DCVC model



Data plotted as mean ± SEM. *** p< 0.001, **p<0.01 Two tailed T-test

SLC6A19i Dose Dependent Target Engagement (uAA's)



SLC6A19i Dose Dependent Protection From DCVC Kidney Damage