First-in-human Translation of a Biomimetic Glyceride Prodrug Platform: Enabling Avoidance of First-pass Metabolism via Lymphatic Absorption

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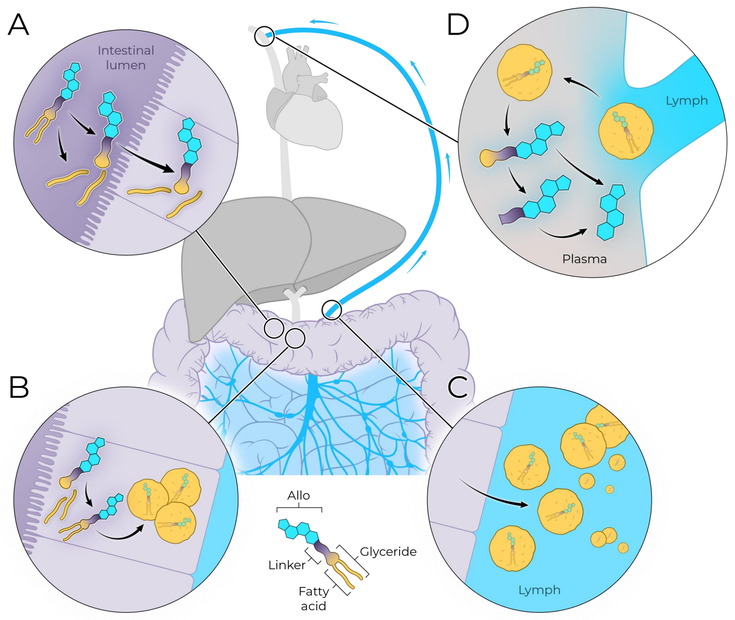
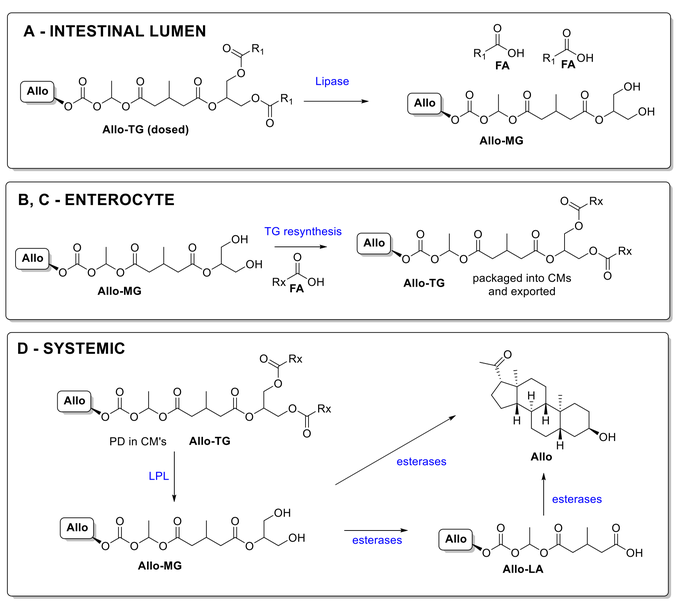
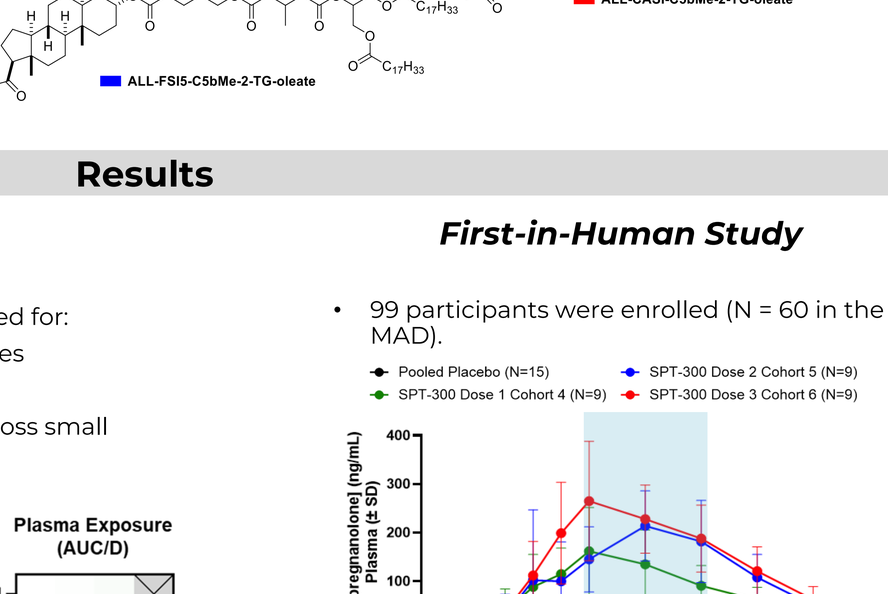
Introduction

- Many potential small molecule drugs with validated human pharmacology are limited by issues such as first-pass metabolism in the gut and liver.
- One example is allopregnanolone, an endogenous neuroactive steroid with validated anxiolytic and anti-depressant activity that has poor oral bioavailability due to first-pass metabolism.
- To address this challenge, the Glyph™ platform conjugates a drug of interest, such as allopregnanolone, to a dietary lipid molecule using proprietary linker chemistries to shift absorption to the lymphatic route.
- Here, we present the translation across preclinical species to pharmacokinetic (PK) and pharmacodynamic (PD) data in a first-in-human clinical study with our allopregnanolone prodrug clinical candidate, SPT-300.

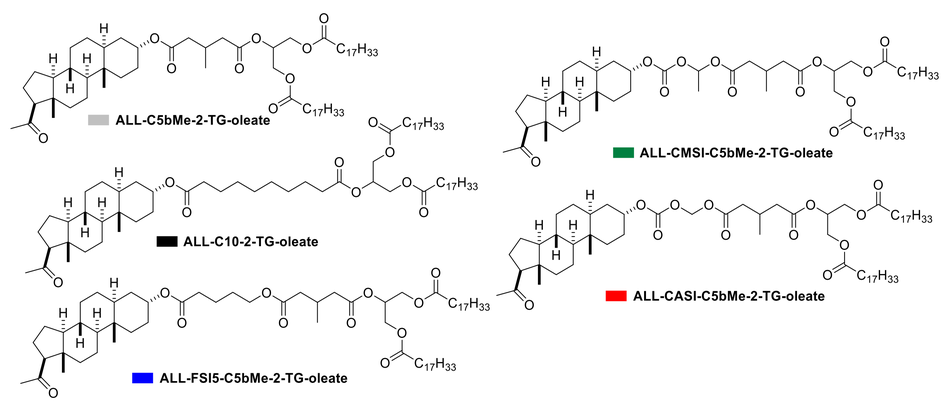




Glyph Platform™ Design

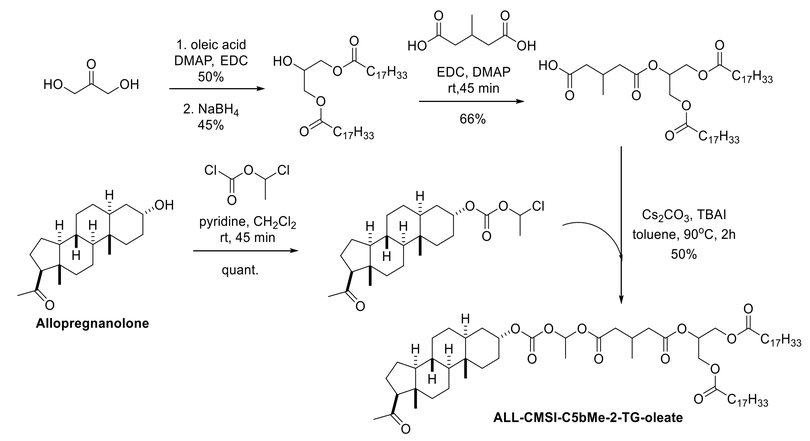


Selected Allopregnanolone Prodrugs



Methods

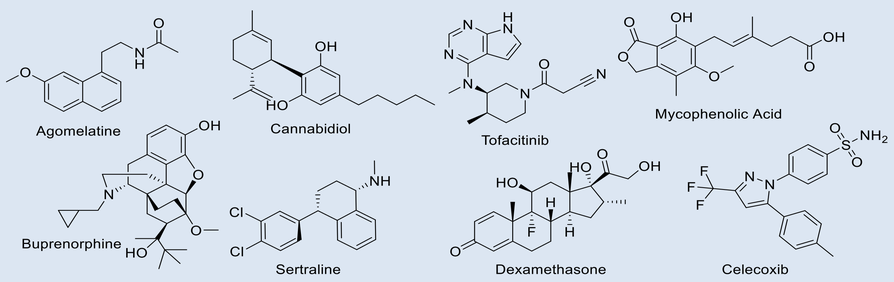
- A series of allopregnanolone prodrugs with different functional linker elements was designed, synthesized (see below), and evaluated by screening for in vitro plasma release across several species, validating lymphatic transport in rodents, and assessing plasma levels after oral administration across small and large animal species. The dose-normalized exposure (AUC/D) is visualized after normalization for body surface area using conventional allometric scaling factors.



- Quantitative whole-body autoradiography studies were performed in rats administered 30 mg/kg of SPT-300. Radiolabeling was performed on the allopregnanolone (Allo label) or the linker (linker label) to ascertain the fate of each element.
- This first-in-human study included double-blind single-ascending dose (SAD), 7-day multiple ascending dose (MAD), and open-label food effect (FE) parts (NCT05129865). SPT-300 was dosed orally, once-daily, either during the day or before bedtime.
- Safety, PK, and PD data were collected across all study cohorts. PD assessments included the Stanford Sleepiness Scale (SSS), quantitative EEG (qEEG)[1] and video-oculography for saccadic eye velocity (SEV).[2]

Beyond SPT-300

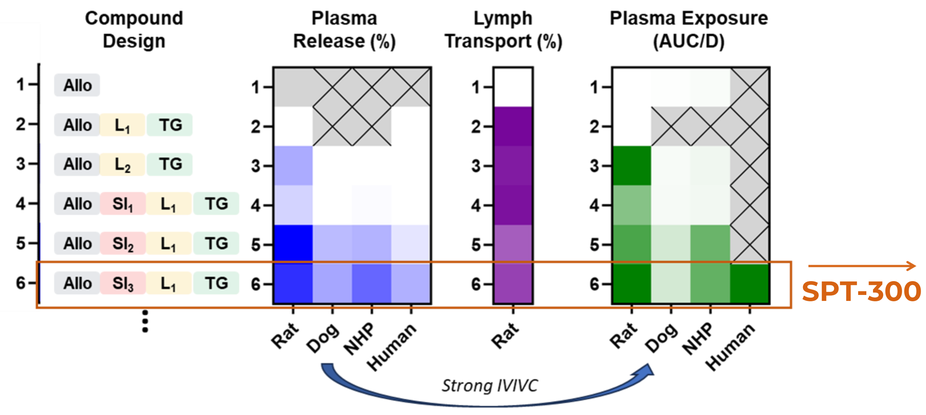
- Compatible with a range of parent API physicochemical properties (e.g., MW, hydrophobicity)
- Demonstrated attachment to a range of functional groups, including alcohols, phenols, carboxylic acids, amines, amides, sulfonamides
- Exemplified with > 20 drugs (selected examples):



Results

Discovery Program

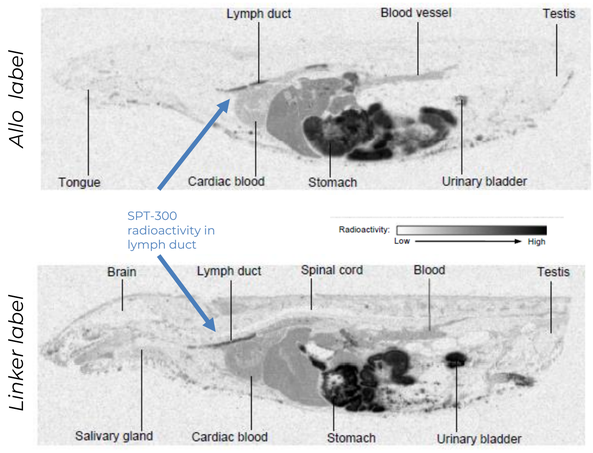
- Assay data for a select subset of prodrugs screened for:
  - in vitro plasma release across several species
  - lymphatic transport in rodents
  - plasma levels after oral administration across small and large animal species

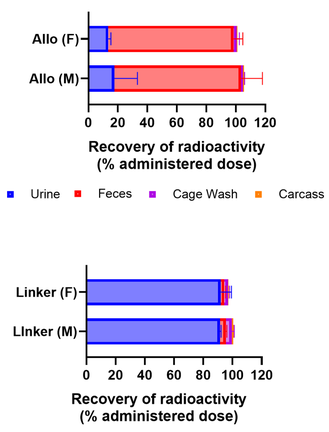


X = prodrug was not assayed in the species indicated.

Preclinical ADME

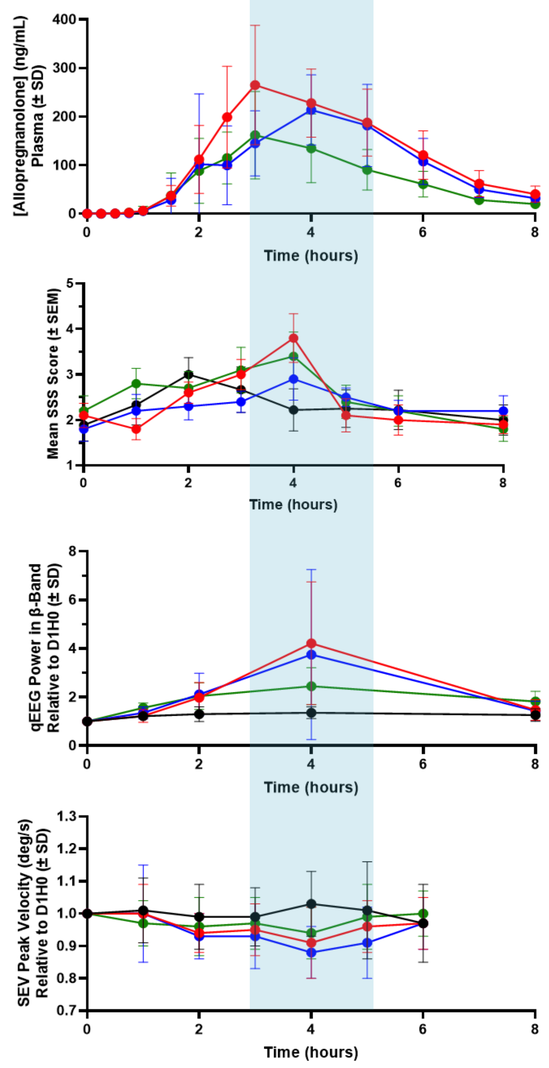
- Radiographic images taken 1 hour after administration clearly show radioactivity in the lymph duct.
- When radiolabeled on the allopregnanolone, elimination is primarily via the feces, consistent with allopregnanolone.[3]
- When radiolabeled on the linker, elimination is primarily renal, consistent with a relatively polar small molecule.





First-in-Human Study

- 99 participants were enrolled (N = 60 in the MAD).



PK/PD

- SSS scores decreased after Day 1 and were comparable to placebo.
- Peak allopregnanolone plasma levels and PD signals were observed at 3-5 hours post-dose, corresponding to peak in:
  - increase in sleepiness (SSS)
  - increase in beta EEG power
  - deflection in SEV at 4h post-dose

Discussion

- The Glyph platform generates new drug candidates from small molecules with validated pharmacology but poor bioavailability or other limitations.
- Dosing of SPT-300 in healthy volunteers resulted in therapeutically relevant plasma exposures of allopregnanolone — along with associated markers of PD activity.
- SPT-300 was generally well-tolerated. Adverse events were dose-dependent and consistent with the pharmacology of GABA.
- Multiple pharmacodynamically active doses will be included in a planned Phase 2b study in major depressive disorder.

References:
1. Christian, Edward P., et al. "EEG-β/γ spectral power elevation in rat: a translatable biomarker elicited by GABAAα2/3-positive allosteric modulators at nonsedating anxiolytic doses." *Journal of Neurophysiology* 113.1 (2015): 116-131.
2. Timby, Erika, et al. "Pharmacokinetic and behavioral effects of allopregnanolone in healthy women." *Psychopharmacology* 186 (2006): 414-424.
3. Sage Therapeutics. *Zulresso*. Food and Drug Administration, 2018.

Disclosures:
JSS, **TQ**, **DKB**, and **MCC** are currently employed by Seaport Therapeutics. **JSS**, **TQ**, **SH**, **LH**, **NLT**, and **CJHP** are coinventors of a lymph-directing glyceride prodrug technology that has been licensed to PureTech Health and Seaport Therapeutics.