

Outstanding questions box

Humans - adjunctive 5-HTP SR to SSRI:

- Efficacious and safety in TRD?
- Daily dose range?
- Adverse event profile and therapeutic index?
- Best embodiment of a 5-HTP SR drug? formulation strategy?
- Particular relevance for specific patient sub-populations?
- Can high-responding patients be pre-identified? based on genetic or physiological biomarkers?
- Relevance for other CNS indications, e.g. anxiety, pain, and neurological disorders?
- Effect on brain connectomics?
- Effects on cognitive bias and mood?
- Regional intestinal absorption?

Animals - adjunctive 5-HTP SR to SSRI, using clinically-relevant SSRI dosing

- Full behavioral characterization and sequelae in animal behavioral models? dose-response relationships?
- Effect on stress responses?
- Neurogenetic, epigenetic, cell signaling, and structural effects?
- Effect on 5-HT receptor function?
- Differential effects under normal and 5-HT deficient conditions?
- Improved modes to model 5-HTP SR in animals? e.g. subcutaneous tablets?
- Mechanism of 5-HTP intestinal absorption? active and/or passive components?

Trends box

Clinical and preclinical evidence suggest that elevating brain extracellular 5-HT (5-HT_{Ext}) in a sustained fashion beyond the effect achieved by a SERT inhibitor treats treatment-resistant depression. Previous such drug strategies all had safety, mechanism, or pharmacokinetics limitations.

Adjunctive 5-HTP strongly and synergistically augments SERT Inhibitor-induced 5-HT_{Ext}-elevation, whereas 5-HTP alone has modest effects. 5-HTP has a good human safety record, but the absorption and elimination of 5-HTP is too rapid for a 5-HTergic antidepressant.

Our mouse data demonstrates that adjunct 5-HTP slow-release (SR) safely, effectively, and in a sustained fashion elevates 5-HT_{Ext} beyond the SSRI effect.

Integrated with a large body of clinical data, our mouse data suggest that an appropriate 5-HTP SR drug would be a safe and effective therapy for treatment-resistant depression.