Development of a QSP Platform to Quantify Benefits of DAAO Inhibition in Schizophrenia

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Introduction

- Schizophrenia is a disabling disorder that affects less that 1% of the worldwide population (Ayano 2016, Patel et al. 2014)
- Symptoms of schizophrenia can be divided into three categories: positive, negative, and cognitive
  - Positive symptoms include hallucinations, delusions, and paranoia
  - Negative symptoms consist of reduced emotion, reduced ability to experience pleasure (anhedonia), a lack of motivation, and a reduced ability to engage in social interaction
  - Cognitive symptoms include poor executive function, impaired ability to focus on objectives, and reduced working memory
- Hypofunctioning of the *N*-methyl-D-aspartate receptor (NMDAR) and reduction of the NMDAR primary coagonist, D-serine, have been associated with the pathophysiology of schizophrenia, particularly the negative symptoms (Gonzalez-Burgos and Lewis 2012, Homayoun and Moghaddam 2007)
- D-amino acid oxidase (DAAO) is a peroxisomal enzyme highly expressed in the cerebellum that metabolizes D-serine (Verrall 2010)
  - Inhibition of DAAO results in increased D-serine and may lead to improvement in negative symptoms of schizophrenia (Pollegioni 2007)
- Clinical studies have demonstrated the benefit of enhancing NMDA signaling through DAAO inhibition
  - Administration of up to 1 g/day of sodium benzoate proved beneficial for patients with schizophrenia (Lin et al. 2017)
  - A weak response to sodium benzoate was observed in refractory patients (Lane et al. 2013), which is consistent with lack of response to systemic administration of D-serine reported in refractory patients (Heresco-Levy et al. 2005)

TAK-831 Background

- TAK-831 is highly selective and potent DAAO inhibitor
- Non-clinical study showed that administration of TAK-831:
  - Resulted in a much greater DAAO occupancy and increased D-serine levels in the cerebellum compared to sodium benzoate
  - Led to a positive effect on cognition and social interaction in rodent cognition and behavioral models
- TAK-831 is currently in development for the treatment of cognitive impairment and negative symptoms of schizophrenia

Overarching Objective

- TAK-831 team needed computational support to select dose regimens for a planned phase 2 study in subjects with stable schizophrenia
  - TAK-831 non-clinical and clinical data from two phase 1 studies, publicly available *in vitro* and animal data as well as clinical data from sodium benzoate and D-serine administration trials were available for modeling activities

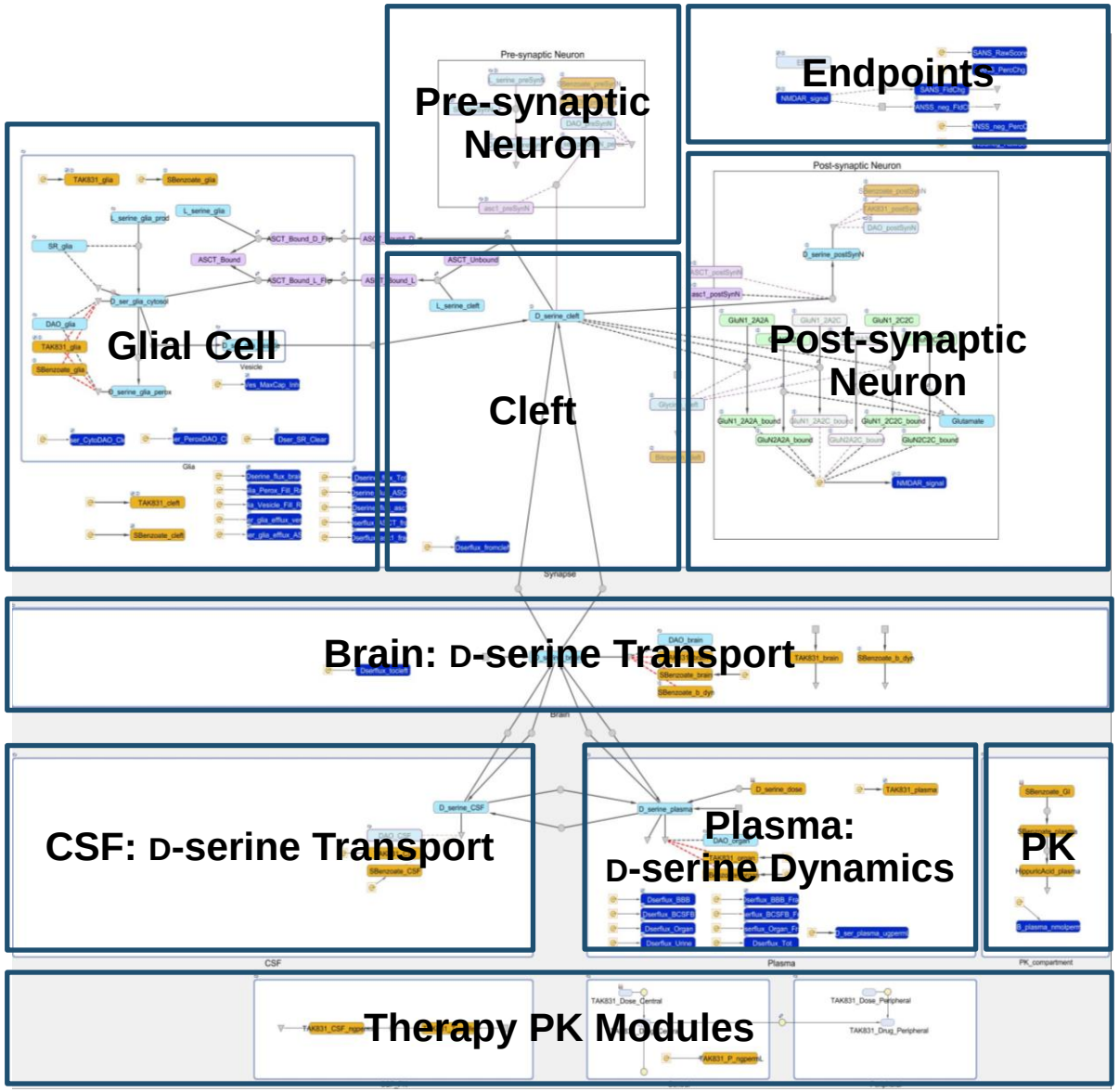
Modeling Strategy

- A QSP model was developed to connect systemic dosing of D-serine and DAAO inhibitors to D-serine increase in the cerebellar synapse to enhancement of NMDAR signaling to clinical outcomes, such as the Positive and Negative Syndrome Scale (PANSS) and Scale for Assessment of Negative Symptoms (SANS)
- The model integrates several compartments, including plasma, cerebrospinal fluid (CSF) and brain compartments, the primary site of DAAO inhibition and a cerebellar tripartite synapse for modulation of NMDAR signaling
- In vitro, animal and human data were used to construct the model, while clinical data from trials with sodium benzoate and D-serine administration were used to ensure consistency of whole-system behavior
- The developed mechanistic platform was used to select dosing regimens for a planned phase 2 trial in subjects with schizophrenia

Platform Development

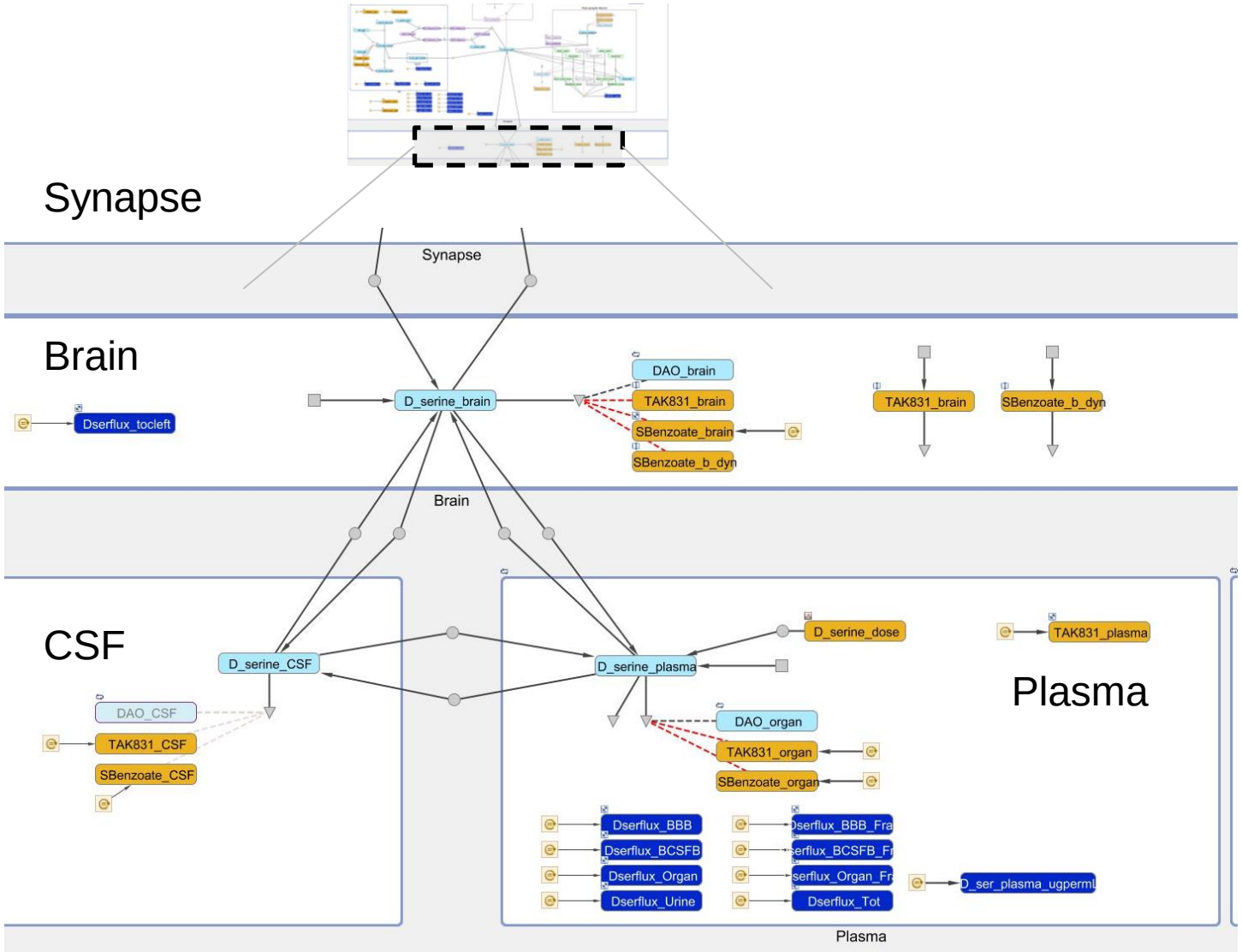
- Stage 1: Building the schizophrenia PhysioMap
  - Define the biological mechanisms that will be modeled mathematically
- Stage 2: Assembling the mechanistic model
  - Stage 2a: Convert biology to equations
  - Stage 2b: Identify parameters and calibrate the model to available data
  - Stage 2c: Set characteristics of virtual patients (VPs)
- Stage 3: Support TAK-831 clinical development
  - Use the platform to guide dose selection for a phase 2 clinical study

Stage 1: The Schizophrenia PhysioMap



- Plasma compartment
  - TAK-831
  - D-serine and sodium benzoate
- CSF compartment
- Brain compartment
- Tripartite synapse in the cerebellum
- Outcome endpoints
  - Positive and Negative Syndrome Scale (PANSS) negative
  - Scale for Assessment of Negative Symptoms (SANS)

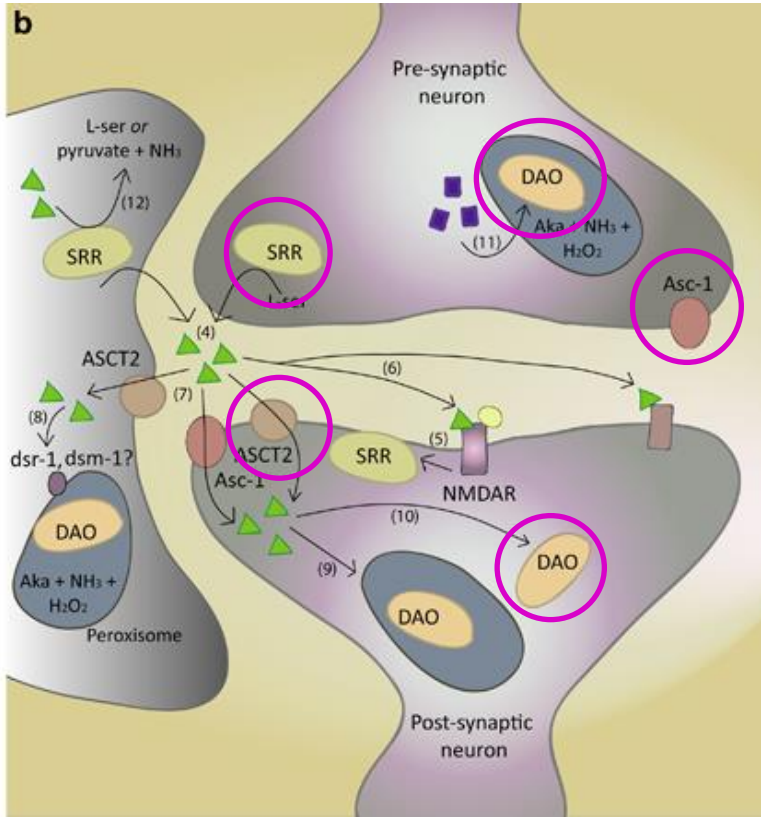
Plasma, CSF and Brain Compartment



- D-serine in plasma and CSF are potential biomarkers of interest
- Brain compartment was added to facilitate D-serine transport equilibrium
  - Inclusion of the brain compartment enabled comparisons of D-serine concentration in plasma, overall brain, cerebellar synaptic cleft and CSF
  - D-serine levels in the brain were estimated by averaging the D-serine levels reported in cerebellum and cerebrum
- Data from D-serine administration trials was used to calibrate systemic D-serine dynamics
- Data from sodium benzoate administration trials was used to calibrate local D-serine dynamics

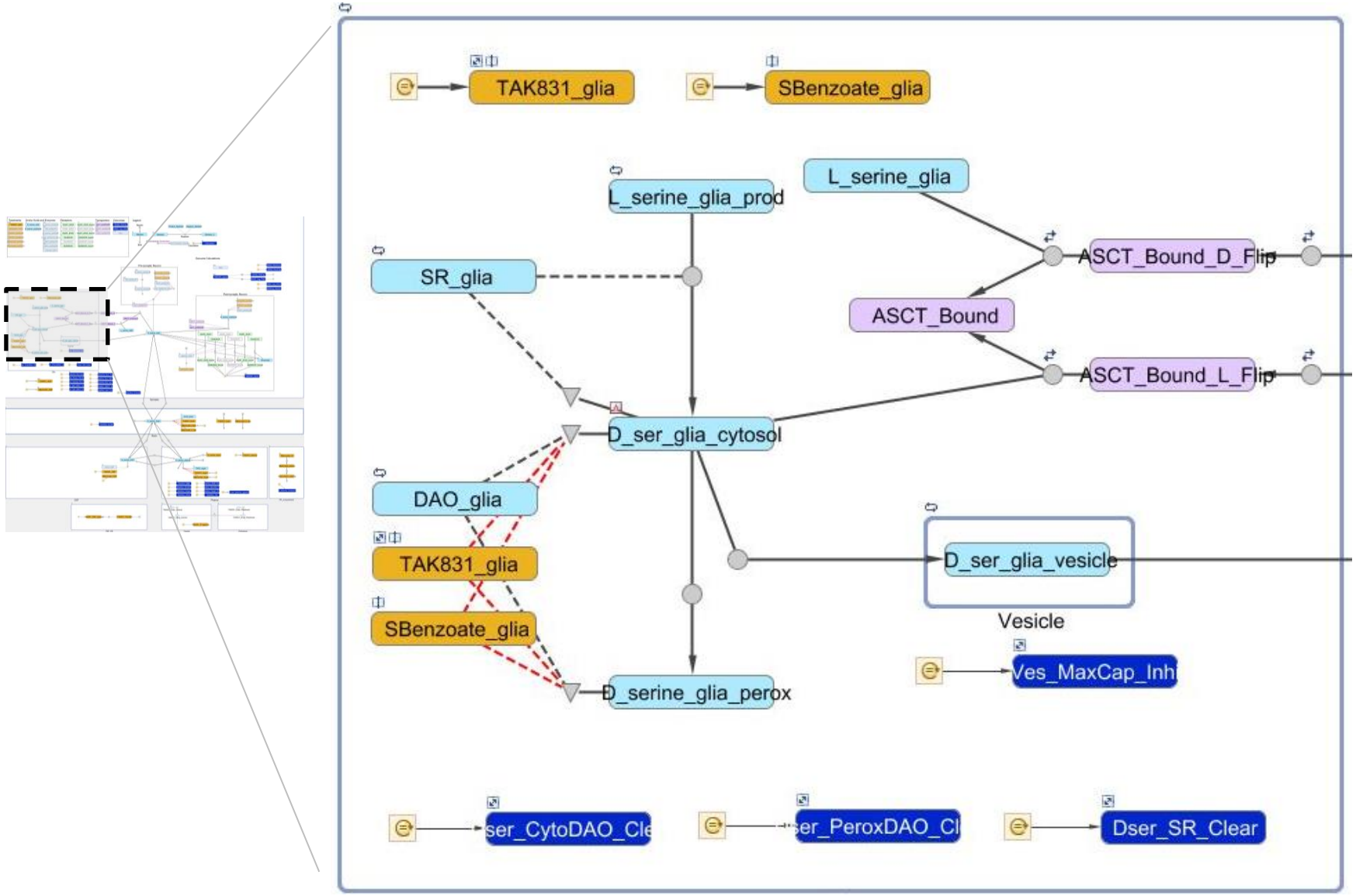
Tripartite Synapse in the Cerebellum

Verrall 2010 PMID 19786963



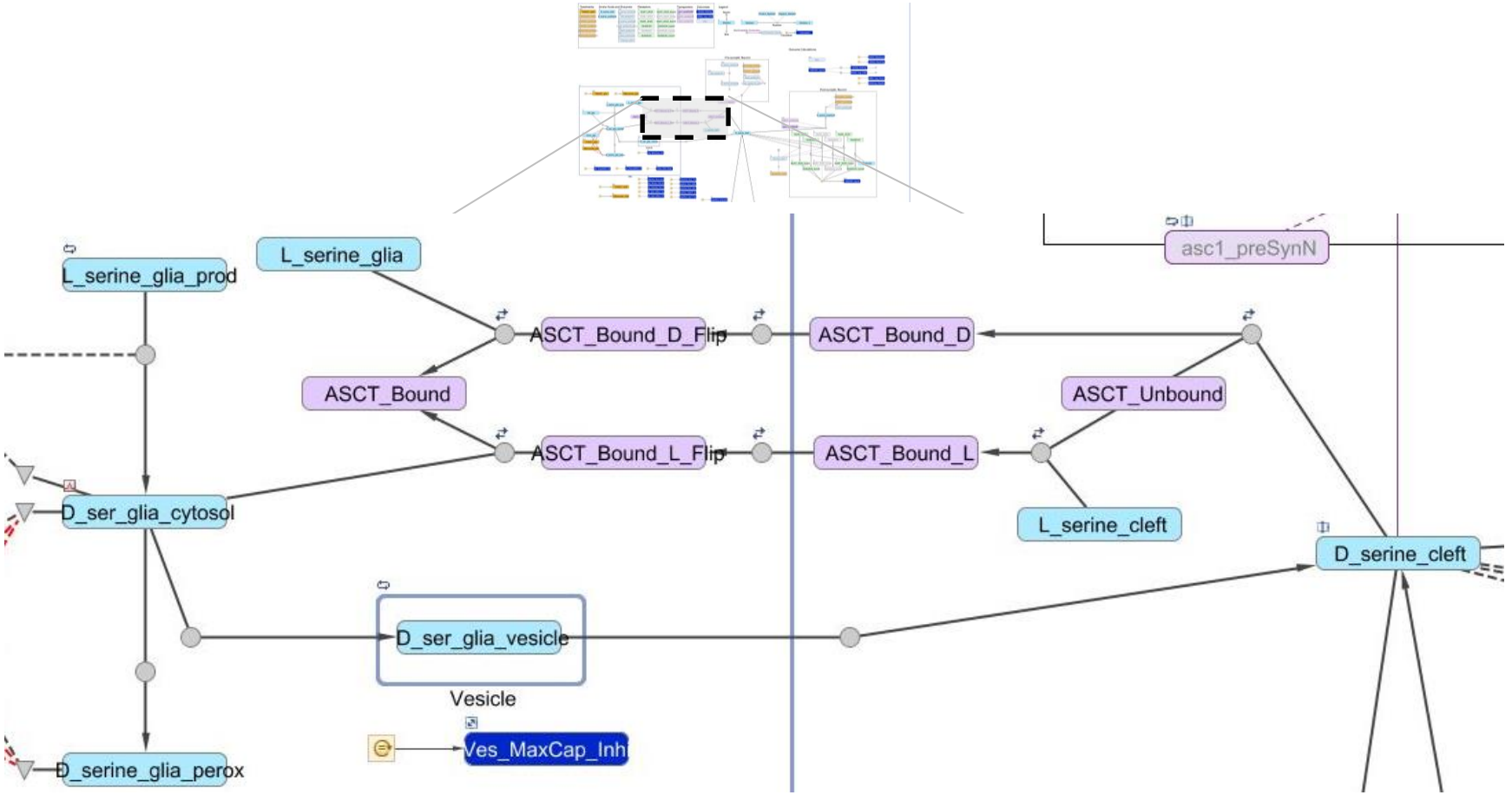
- D-serine is synthesized by serine racemase and broken down by DAAO in glial cells
- D-serine is transported out of the glia and into the synapse by vesicle release and transported back via the ASCT2 transporter
- Additional pathways (outlined in purple) might be active in cerebellum
  - Included in the PhysioMap for future explorations, but not quantified in the current project

Biology of Glial D-Serine



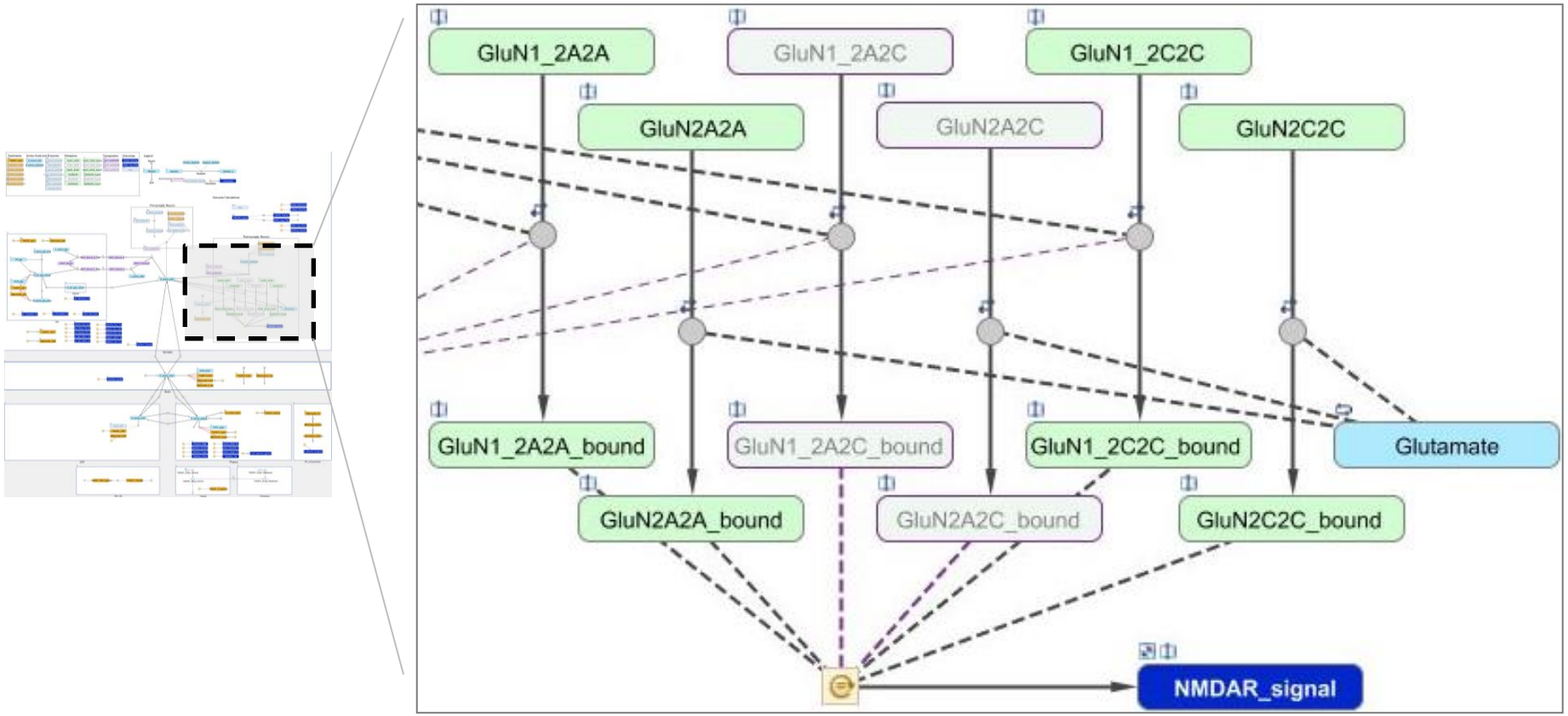
- Cytosolic D-serine is produced from L-serine via serine racemase
- Cytosolic D-serine is degraded via the peroxisome and transported into the cerebellum via vesicular release
- Both L-serine and D-serine are transported back into the glial cells from the cerebellum via active transport (antiporter model)

Antiporter Model was Used to Elucidate D-Serine Transport into the Glia via ASCT



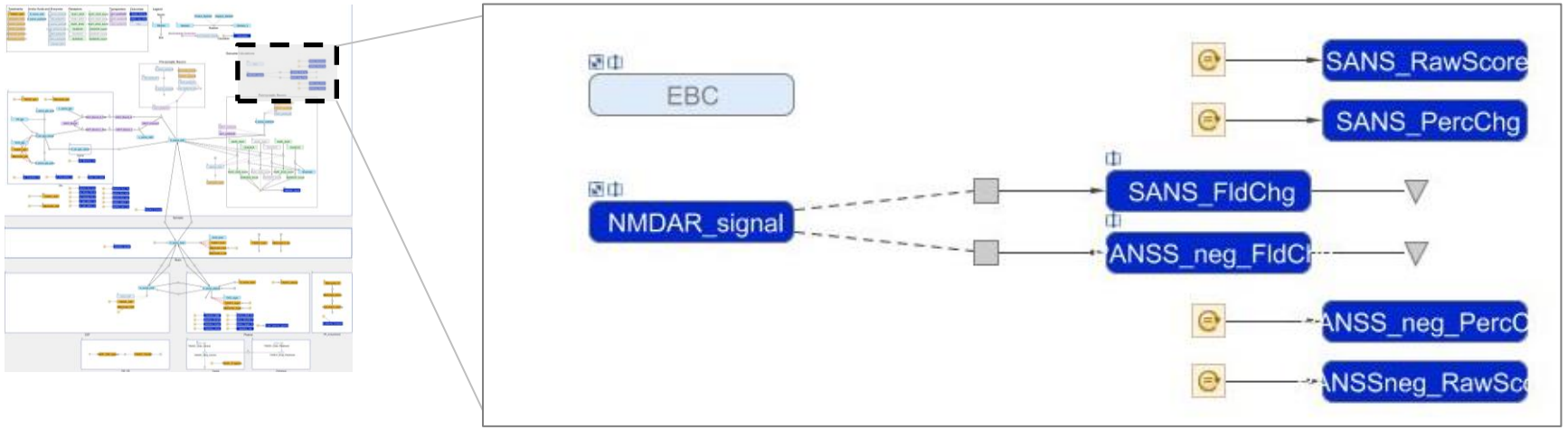
- Implemented the active transport in an alternating-access antiporter model (Zuckerman)
- Calibrated the model to match available data (Ribeiro 2002 PMID 11864625)

Modulation of NMDA Receptor



- N2A and N2C are expressed in adult brain (Rubio 2012 PMID 24116269) and predominant in cerebellum of patients with schizophrenia (Schmidt 2010 PMID19856012)
- The distribution/expression levels of N2A2C heterodimers is unknown and have been inactivated

Linking NMDA Signaling to Clinical Endpoints



- An empirical E_{max} model was used to map activation of NMDAR signaling into improvement of negative symptoms (PANSS, SANS) and cognitive symptoms (Eye Blink Conditioning)

Stage 2: Assembling the Mechanistic Model

- Stage 2a: Convert biology to equations
  - Convert the PhysioMap into the modeling platform by adding equations and generic parameters
  - Include pharmacokinetic models and mode of action for TAK-831 and comparator therapies
- Stage 2b: Parameterize the model
  - Calibrate all subsystems to be consistent with relevant data
  - Integrate all subsystems and refined parameter values to ensure consistency of whole-system behavior
- Stage 2c: Characteristics of virtual patients (VPs)
  - Create a reference virtual patient of the desired phenotype (baseline parameterization) and variations to the reference VP (alternative parameterizations) to predict the variability of endpoints observed in clinical trials

Stage 2a: From Biology to Equations

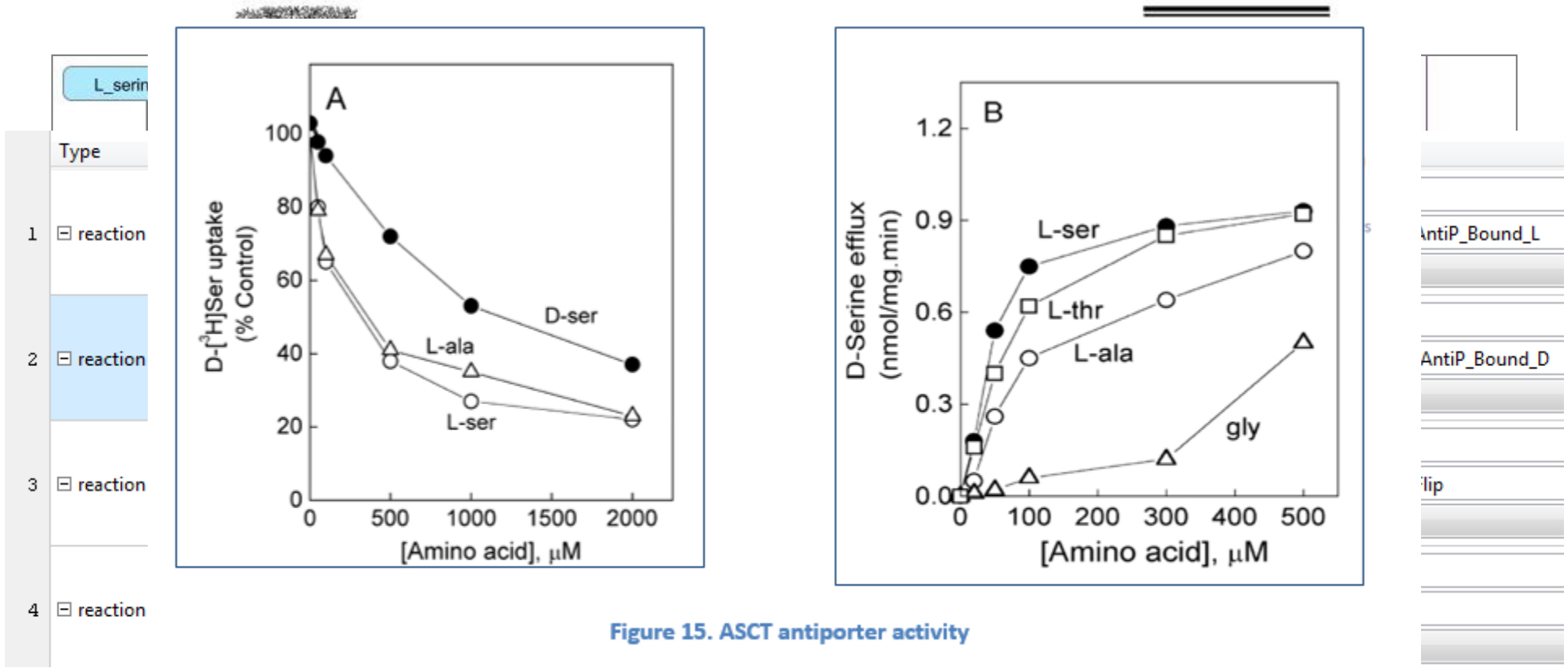


Figure 15. ASCT antiporter activity

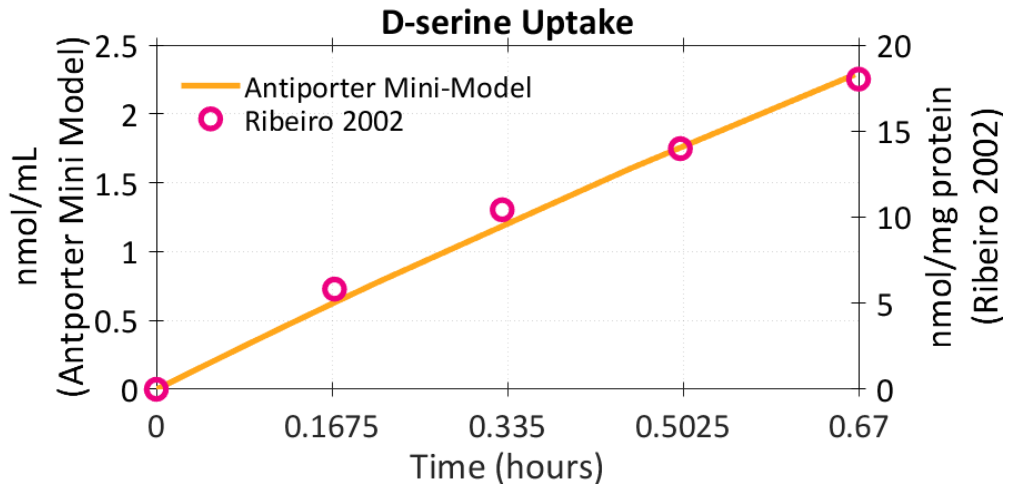
From (Ribeiro et al. 2002)

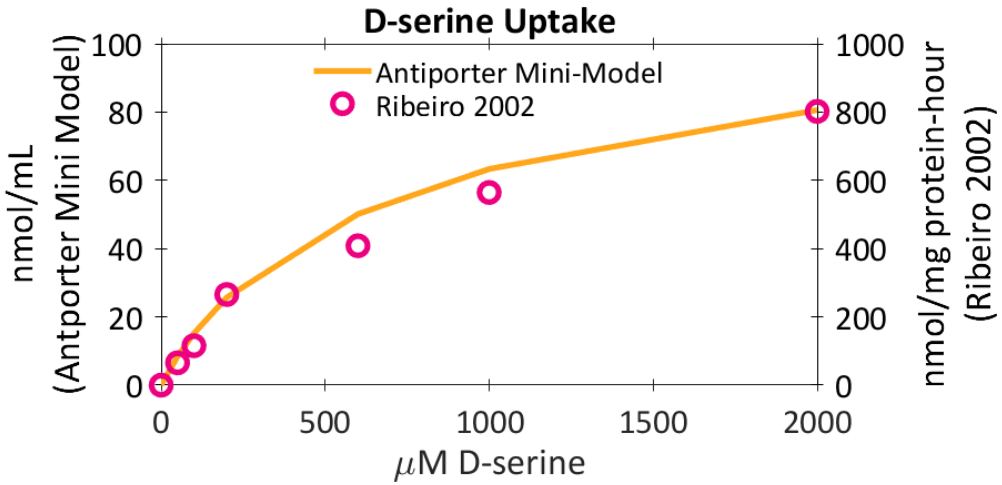
D-serine uptake via ASCT in cultured astrocytes is inhibited by presence of other amino acids in media (left). D-serine efflux is increased by the presence of other amino acids in media (right)

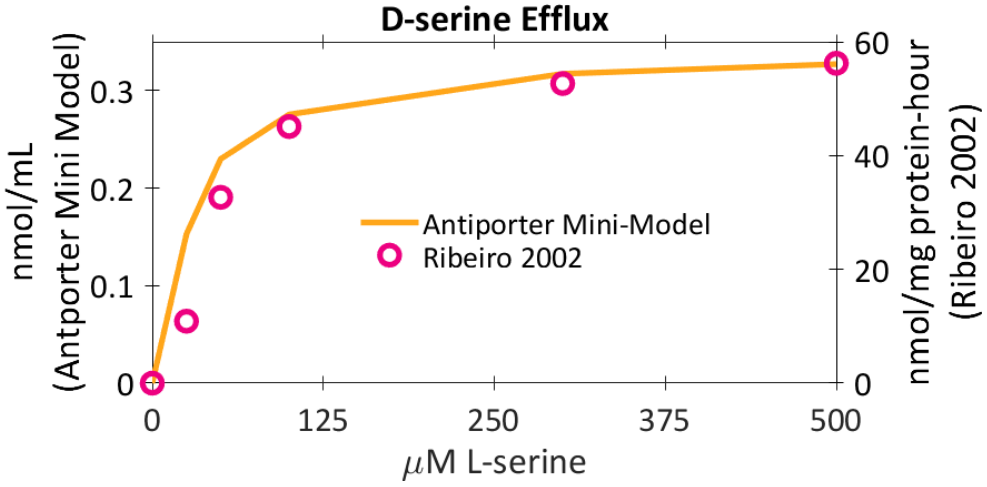
Stage 2b: Model Parameterization

- Several parameters were obtained from the literature
- Remaining parameters were obtained using in house and available *in vivo* and clinical data
  - Antiporter model, TAK-831 data in rats and human, sodium benzoate and D-serine clinical studies

Antiporter Model Captures D-serine Transport Dynamics

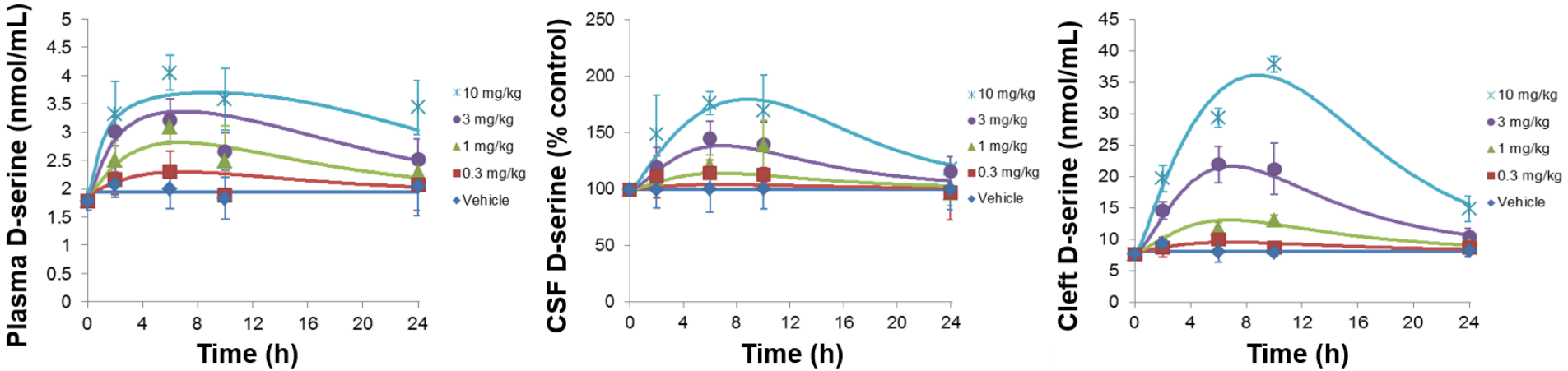




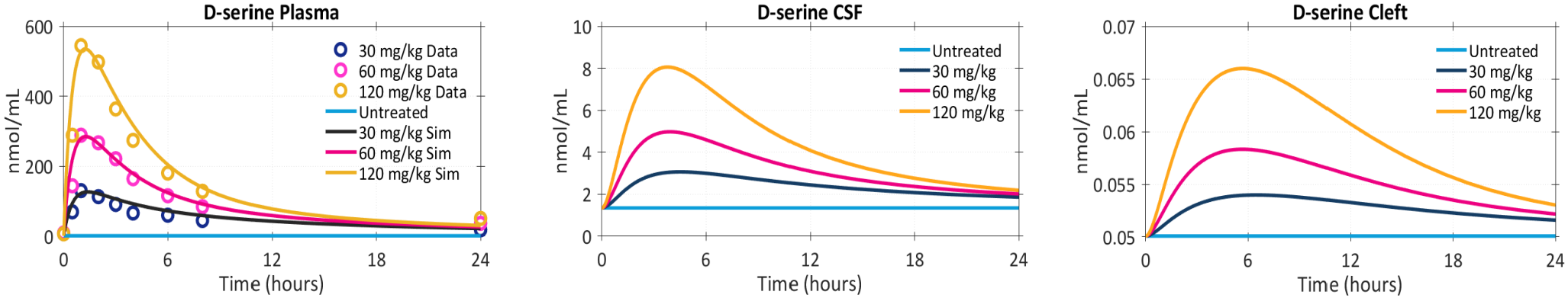


- Data from Ribeiro (2002 PMID 11864625) were used to calibrate transporter kinetics

Model Calibration Using TAK-831 Rat Data

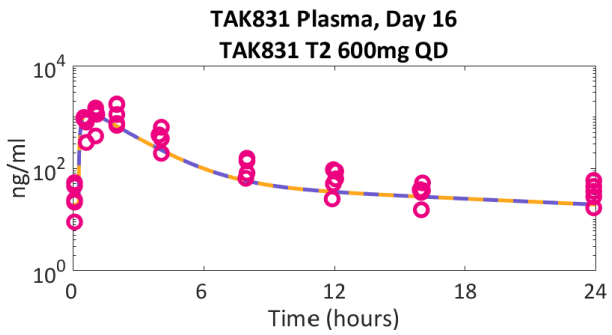


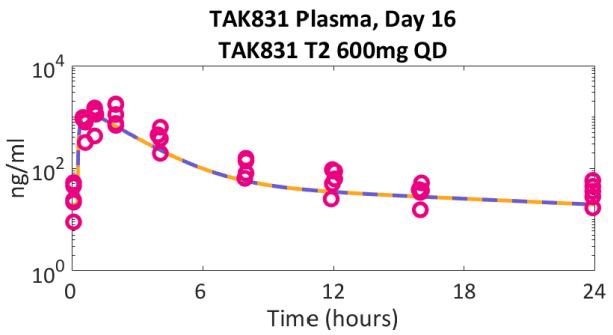
- Acute dosing of TAK-831 in rats indicated that:
  - Degree of D-serine increase is similar in plasma and CSF, with only a slight delay into CSF
  - Degree of D-serine increase in cerebellum is greater than in plasma and CSF, with similar time profile as CSF

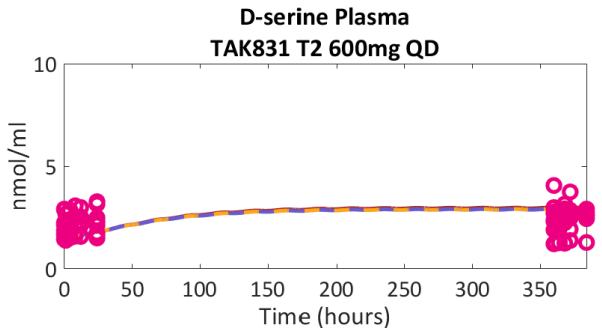


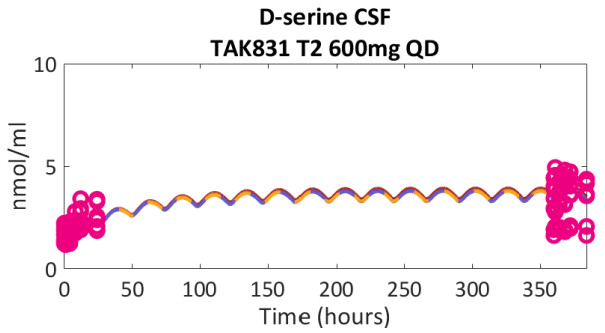
- Model was fit to available D-serine plasma data in humans (Kantrowitz 2010)
  - Simulated D-serine levels in CSF and cleft were consistent with *in vivo* data

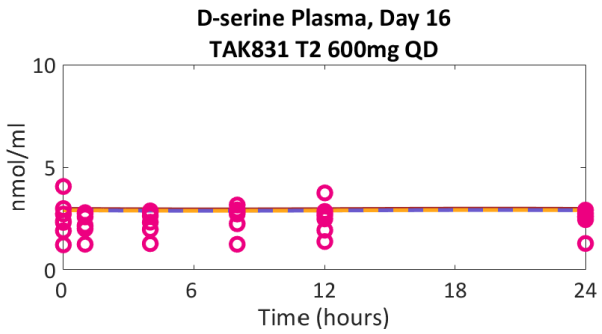
Model Calibration Using TAK-831 Clinical PK Data

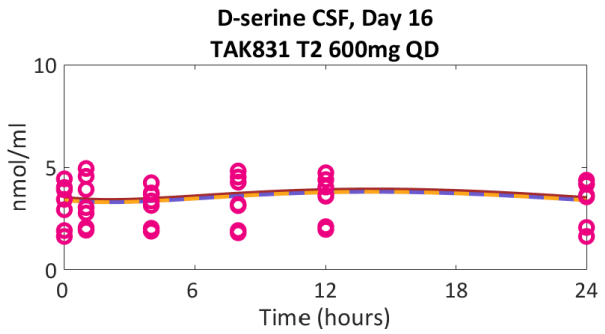






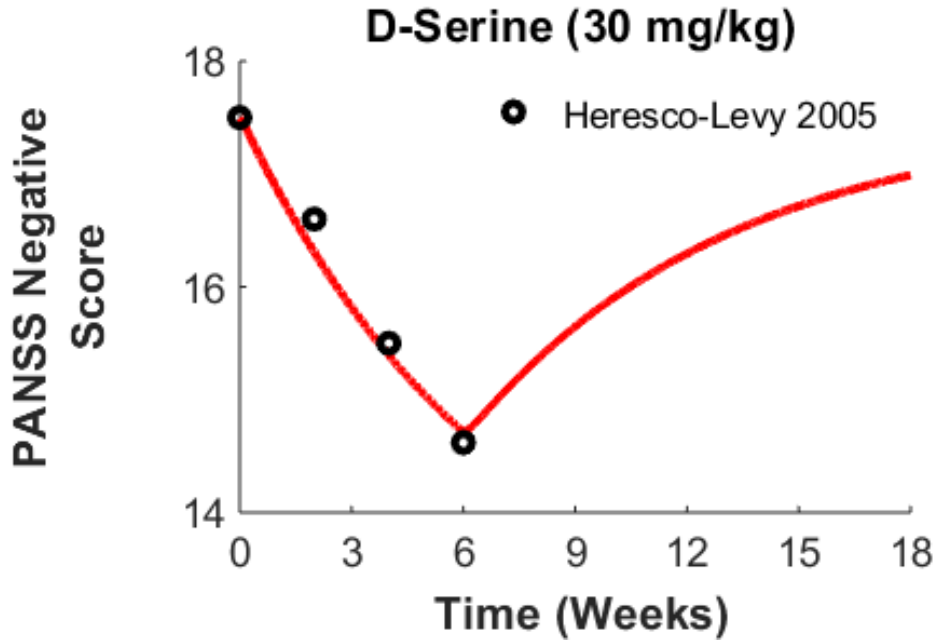


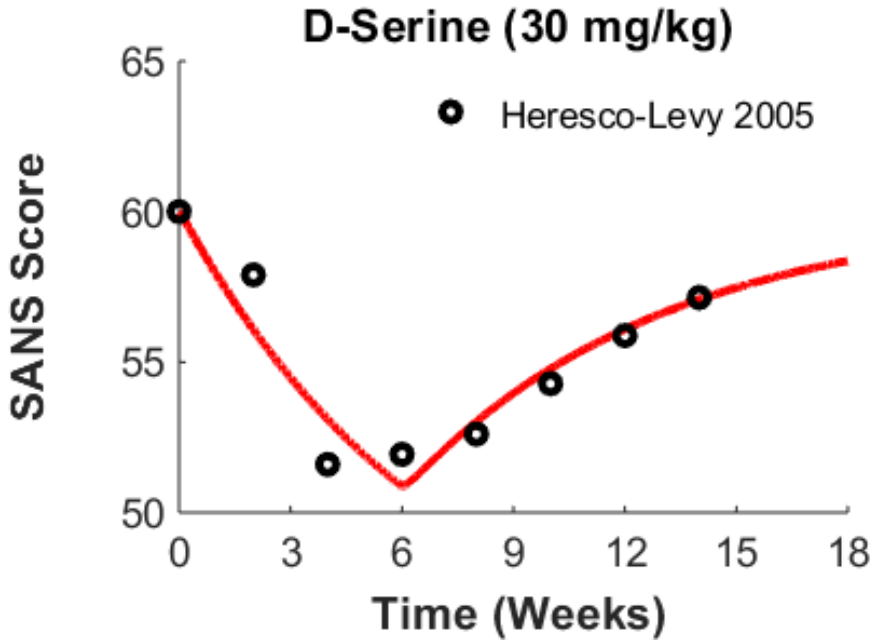




- Model properly describes the dynamics of D-serine in plasma and CFS after TAK-831 administration

Model Calibration Using D-serine Clinical Data





- Model adequately describes changes in PANSS negative and SANS scores following administration of D-serine in patients on a risperidone background (Heresco-Levy 2005)

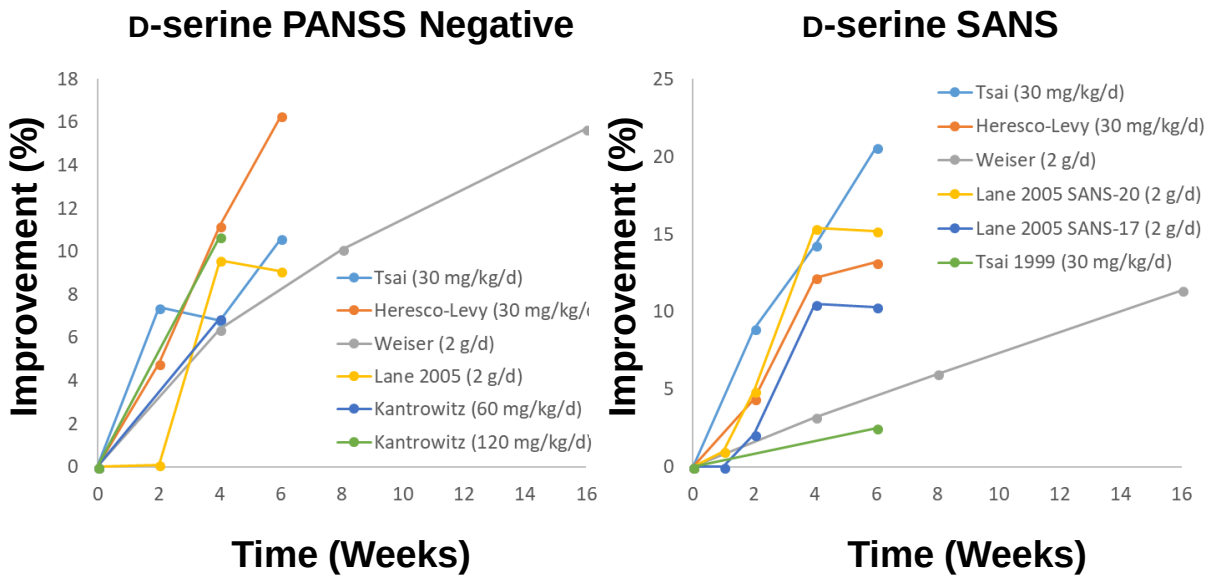
Stage 2c: Characteristics of Virtual Patients (VPs)

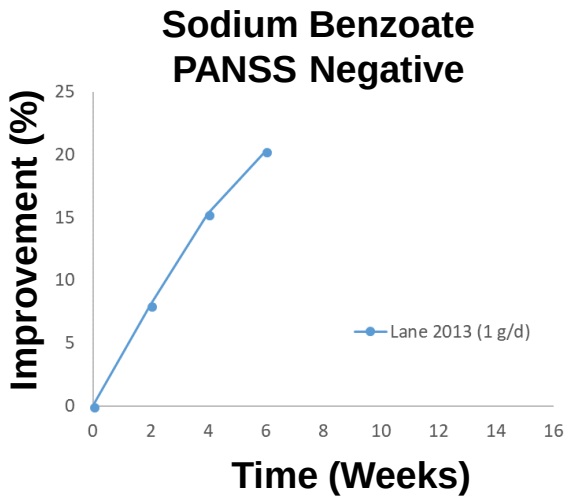
- Model calibration provides the reference virtual patient
  - Set of parameters describing the pathophysiology of an observed phenotype
- However, uncertainties in known biology and model parameters as well as inter-individual and inter-study variability result into a variety of observed phenotypic responses
  - Platform is developed by constructing variations of the reference virtual patient to describe the ranges of observed phenotypes
- Twenty virtual patients were constructed to account for variability/uncertainties and recapitulate the range of PANSS and SANS outcome reported in clinical studies of D-serine and sodium benzoate

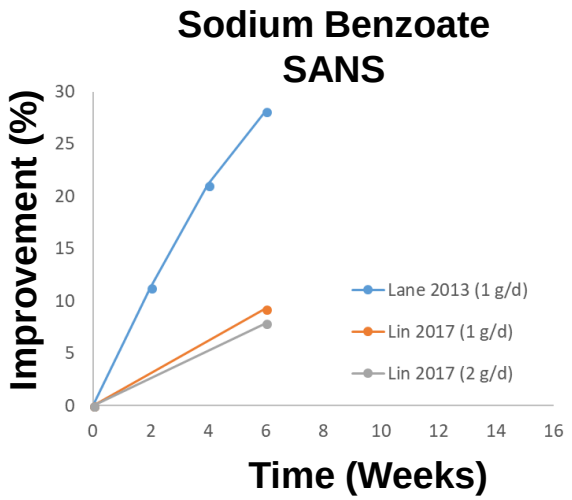
Summary of Clinical Studies

Reference	Patients, Medications, Illness Duration (yrs)	Tx	Dose	Duration	Outcomes Reported	Notes
Lane 2013 PMID 24089054	n= 52 Taiwanese, typical/atypical, (15.8)	Sodium Benzoate	1 g/d	6 wks	• PANSS negative • SANS	
Lin 2017 PMID 24089054	n=20 Chinese, refractory, on clozapine, (20.5)	Sodium Benzoate	1 g/d 2 g/d	6 wks	• PANSS total • SANS	Only refractory schizophrenics
Kantrowitz 2010 PMID 20541910	n= 12, 19, 16, Chlorpromazine or equivalent, (19.8-22.4)	D-serine	30 mg/kg 60 mg/kg 120 mg/kg	6 wks	• PANSS negative • Plasma D-serine Cmax and ave 24-hr at wks 1,4	Patients with ≥ 2 antipsychotics and/or clozapine excluded
Tsai 1998 PMID 15780844	n= 14 Taiwanese, Chlorpromazine or equivalent, (9.8)	D-serine	30 mg/kg	6 wks	• PANSS negative • SANS • Plasma D-serine 2,4,6 wks	Relatively short duration of illness
Heresco-Levy 2005 PMID 15780844	n=39, risperidone or olanzapine, (22.5)	D-serine	30 mg/kg	6 wks	• PANSS negative • SANS • Total serine plasma	
Weiser 2012 PMID 22795211	n= 195, typical/atypical, (17.1)	D-serine	2 g/d	16 wks	• PANSS negative • SANS	Not significant vs. placebo
Lane 2005 PMID 16275807	n= 65, Risperidone, (7.5)	D-serine	2 g/d	6 wks	• PANSS negative • SANS	Relatively short duration of illness
Tsai 1999 PMID 10553752	n=20, refractory, on clozapine, (20.6)	D-serine	30 mg/kg	6 wks	• PANSS total • SANS	No improvement, refractory patients

Improvements in PANSS Negative and SANS in D-Serine and Sodium Benzoate Studies





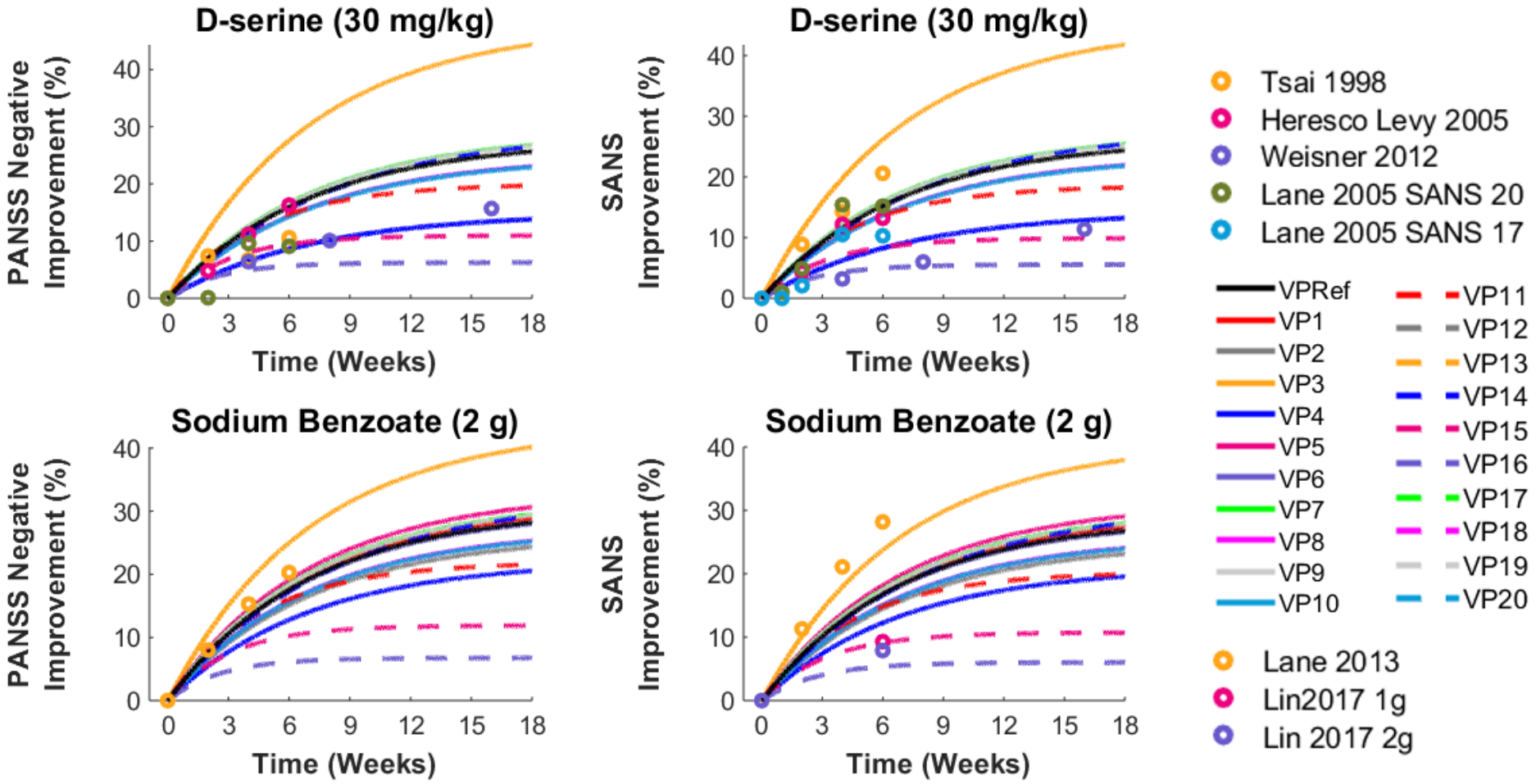


- Although D-serine reaches steady state within days, most studies show benefits increasing over weeks, suggesting a cumulative benefit
- % improvement is greater for SANS, suggesting this score is a more sensitive clinical outcome
- Clinical response to sodium benzoate appears to be on similar order of magnitude as to D-serine
- D-serine and sodium benzoate dose-response are not clear from these studies
  - Uncertainty in predicting clinical scores after 6 weeks

Setting Characteristics of Virtual Patients

VP	Mechanistic Change	Does mechanism directly impact DAO activity?	How is DAAO activity impacted?
1,2	Changes in D-serine production in the glia, balanced by changes in peroxisome uptake	Yes	Higher/Lower concentration of D-serine in the glia peroxisome where DAAO is more concentrated
3,4	Changes in flux of D-serine from whole brain, balanced by changes glial vesicular release	Yes	Higher/lower rate of D-serine leaving the glia where DAAO is localized
5,6	Changes in vesicle maximum capacity, balanced by decreased glial cytosol release	Yes	More/Less D-serine is sequestered away from DAAO in the glia
7,8,9,10	Changes in GluN1-2x2x EC50, balanced by changes in GluN1-2x2x dissociation rates	No	--
11,12,13,14	Changes in PANSS/SANS EC50, balanced by changes in PANSS/SANS degradation rates	No	--
15, 16	Changes in amplification of NMDA signaling, balanced by changes in scoring degradation rates	No	--
17,18,19,20	Changes in SANS and PANSS baseline scores	No	--

VPs Capture Range of Clinical Scores for D-Serine and Sodium Benzoate Studies

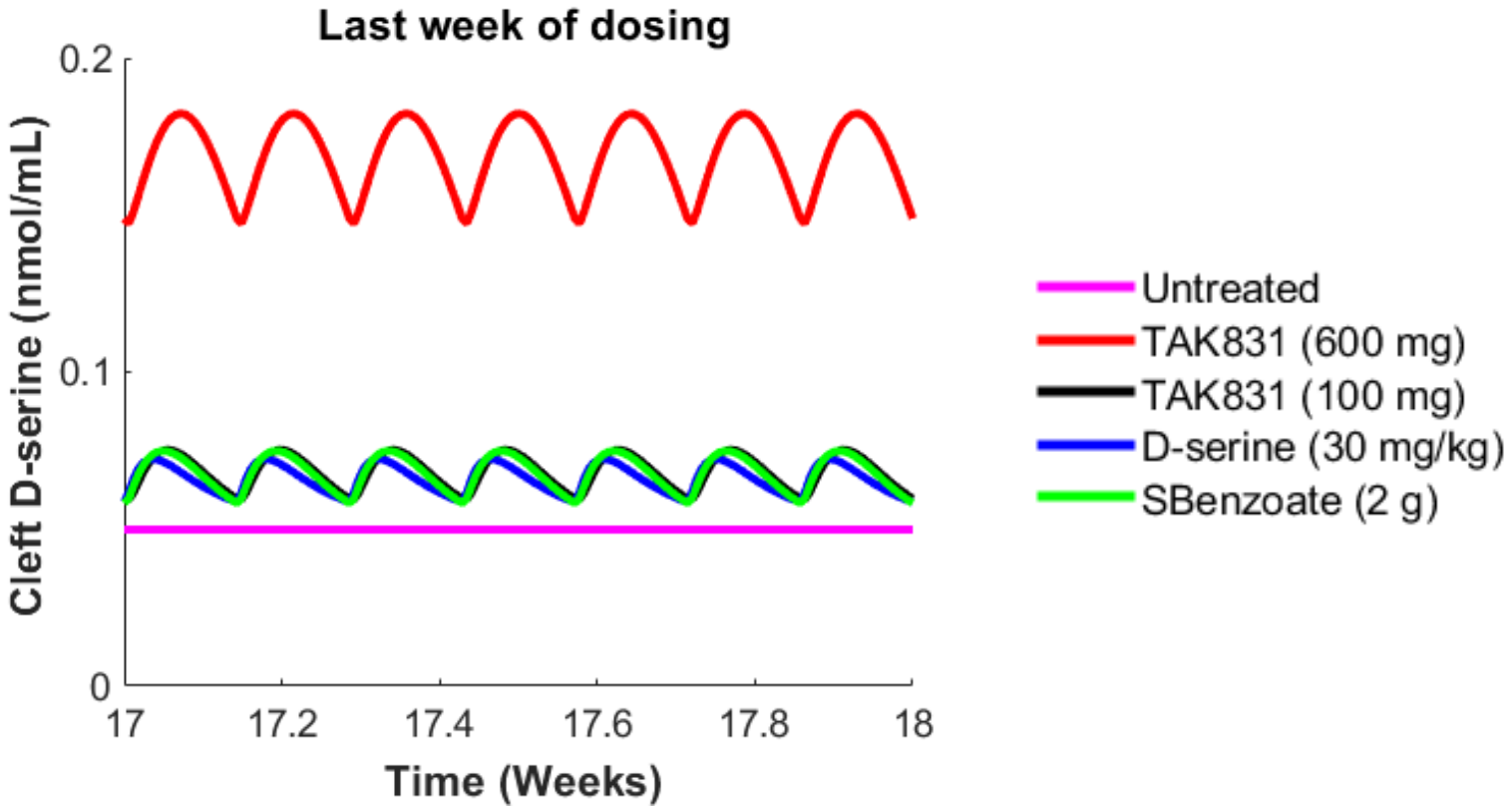


- Uncertainty the in the dose-response has an impact on the degree of improvement that can be achieved by increasing cleft D-serine and NMDA signaling

Stage 3: Support Clinical Development of TAK-831

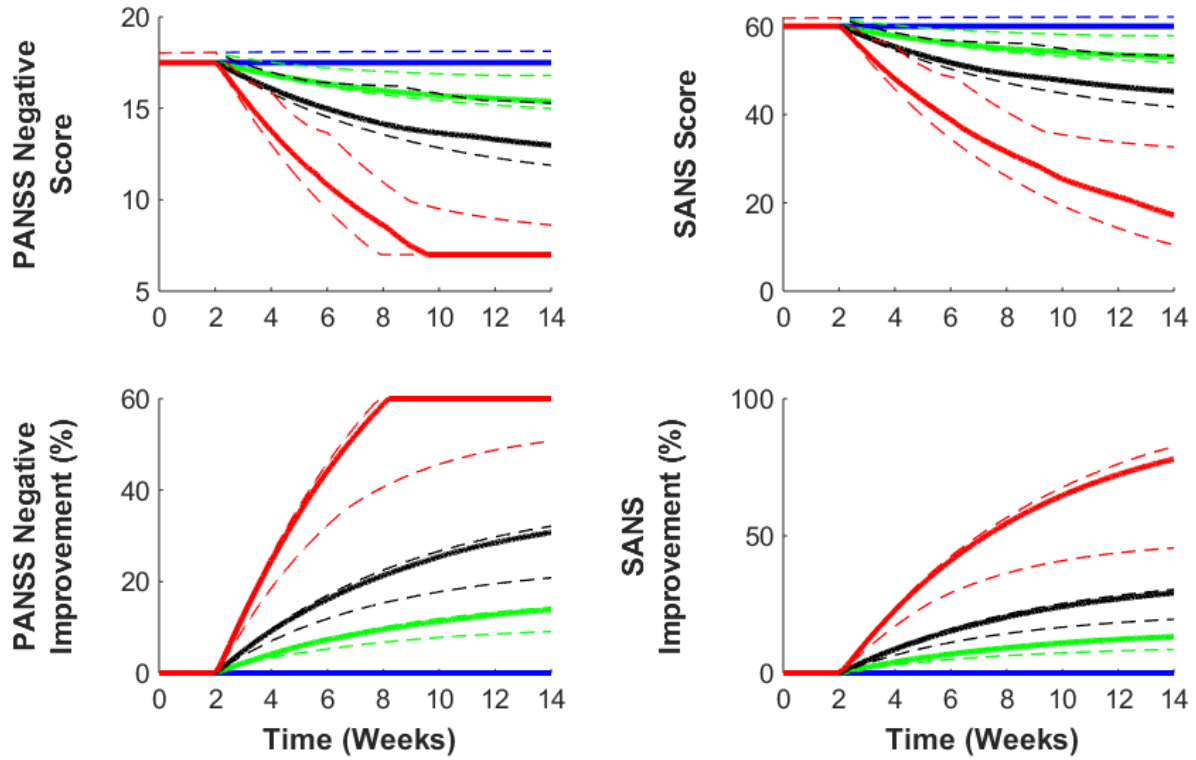
- Predict levels of D-serine in the cleft in response to doses of TAK-831
- Guide dose selection for a planned phase 2 study in subjects with stable schizophrenia

Comparison of Cleft D-serine Across Therapies After Chronic Daily Administration



- Modeling results suggested that daily administration of 100 mg of TAK-831, 2 mg of D-serine, and 30 mg/kg of sodium benzoate produced similar elevations of cerebellar D-serine
- Administration of 600 mg of TAK-831 is predicted to significantly increase D-serine levels in the cleft compared to D-serine and sodium benzoate

Simulating TAK-831 ePOC Phase 2 Study



Solid lines:
Predicted Median

Dashed lines:
[20-80] predicted intervals

- Placebo
- TAK831 (50 mg)
- TAK831 (125 mg)
- TAK831 (500 mg)

- TAK-831 is predicted to have a strong impact on symptom scores
  - The empirical relationship between NMDA signaling and symptom scores is not well constrained by data beyond ~20%, so there is uncertainty in the quantitative predictions
- 500 mg of TAK-831 was selected as the highest dose for a planned phase 2 clinical study
  - Daily administration of 125 mg of TAK-831 was included to validate the equivalency in response between therapies
  - Daily dose of 50 mg of TAK-831 was added to investigate the potential existence of an inverted U-shaped response

Summary and Conclusions

- A QSP platform was developed to quantify the benefits of DAAO inhibition in schizophrenia
  - Relevant biology was scoped out
  - Model was calibrated using available pre-clinical and clinical data
  - Inter-study variability and biological uncertainty were accounted for by constructing virtual patients
  - Model qualification will be performed using the results from the on-going TAK-831 ePOC study

- The platform was used to recommend dose regimens for the planned phase 2 clinical study
  - 500 mg of TAK-831 was selected as the highest dose to be administered

- The platform will be:
  - Used to evaluate the suitability of plasma and CSF D-serine as a predictive marker of TAK-831 effects
  - Expanded modularly to support clinical development of additional therapeutics targeting NMDAR function

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Questions