Discovery of Allosteric Modulators of GABA<sub>A</sub> Receptor for CNS Disorders

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Meeting: Keystone Symposium. Brain Therapeutics: Disruptive Technologies and Opportunities. February 16-19, 2020
Session: Integrating Novel Medicinal Chemistry Approaches Targeting the Brain
Disclaimer

Dr. Blanco is an employee of Sage Therapeutics, Inc. with stock/stock options.

Zuranolone (SAGE-217) and SAGE-324 are investigational compounds and are not approved for any use.

Brexanolone injection is approved for the treatment of PPD in adults by the United States Food and Drug Administration. It is not approved for the treatment of essential tremor or any other use.
Seeing the brain differently makes a world of difference
Outline

1. Introduction: Sage’s Differentiated Approach to Drug Development
2. Sage’s approach with GABA_A R Positive Allosteric Modulators (PAMs)
3. Next generation GABA_A R PAMs
Sage Therapeutics

Developing innovative treatment options with the potential to transform the lives of people with brain health disorders

<table>
<thead>
<tr>
<th></th>
<th>APPROVED PRODUCTS</th>
<th>CLINICAL CANDIDATES</th>
<th>THERAPEUTIC AREAS</th>
<th>LIBRARY COMPOUNDS</th>
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Rethinking Neuroscience

*Bridging translational science & experimental medicine*

**Translational Neuroscience**
- Identify functional biomarkers in animals
- Establish genetic and biochemical criteria to select patient populations
- Translate insights between compounds and indications for better odds of success across pipeline

**Experimental Medicine**
- Conduct human studies
- Leverage opportunities to inform development strategy for Sage programs and compounds
- Deliver new biomarkers (physiological / biochemical / genetic)
Sage’s Differentiated Approach to Drug Development

Rethinking Neuroscience
Sage’s distinct integrated approach

- By following the science and designing efficient trials, Sage pursues serial de-risking
  - Data from completed studies on dosing, tolerability, biomarkers inform design of new trials
  - Studies are designed to bridge the gap from targets in context to therapeutic utility
  - De-risking strategy can be used for either the same molecule or a related molecule from the Sage pipeline
  - Target small, focused indication studies with opportunities to expand into larger therapeutic indications

Zuranolone
(SAGE-217)

GABA<sub>A</sub> PAMs
Bridge
NMDA PAM

SAGE-324
SAGE-718

Zuranolone. "International Nonproprietary Names for Pharmaceutical Substances" WHO Drug Information. 32 (4). 2018
GABA<sub>A</sub> Receptors Mediate both Phasic and Tonic Inhibition<sup>1,2</sup>

Why Allosteric Modulation?

- **Positive allosteric modulation (PAM)** increases receptor efficacy and/or potency
- Fine tunes receptor activity without overstimulation
  - Direct gating compounds can’t do this
- Offers potential for significant advantages, high selectivity and minimal off-target effects
Sage’s approach:

• **Synaptic GABA$_A$** receptors mediate **phasic inhibition** whereas **extrasynaptic GABA$_A$** receptors regulate **tonic inhibition**

• **Tonic inhibition** plays a critical role in regulating neuronal circuit excitability
  - Potential to treat multiple diseases not accessible with benzodiazepines

• **Neuroactive steroids** (NAS) enhance activity of BOTH synaptic and extrasynaptic GABAA receptors, unlike benzodiazepines which modulate synaptic GABAA receptors

• Certain Sage NAS compounds demonstrated capability *in vitro* to increase extrasynaptic GABAA receptor trafficking\(^1\)

\(^1\)Modgil et al, *Neuropharmacology*, 2016
Neuroactive Steroids (NAS)

**Endogenous/Natural**
- 24(S)-hydroxycholesterol
- Desmosterol
- Allopregnanolone
- THDOC
- Progesterone
- Pregnanolone

**Synthetic**
- Alphaxolone
- Alphadolone
- Minaxolone
- Ganaxolone
- ORG-20599
- SGE-201

SGE-201 is a key Sage tool compound for PoC and therapeutic utility
Evolution of Neuroactive Steroids

Pre-Sage Status of GABA\(_A\)R PAM NAS Knowledge Base

- NAS class undruggable (orally)
- Poor understanding of the pharmacology
- Difficult to measure biologic activity
- NAS hard to synthesize
- Poor solubility, hard to formulate
- Little or no bioavailability

Sage Advancement of the GABA\(_A\)R PAM NAS Platform

- Zuranolone, SAGE-324
- Discovery of metabotropic effects of NAS GABAAR PAMs: amplification of effects on extrasynaptic GABAARs by increasing their surface expression
- Well developed high throughput assays
- Rapid efficient synthesis with access to all areas of scaffold for SAR
- Developed formulations for IV, IM, PO of multiple compounds (solution and solid)
- Highly bioavailable, fit for purpose

Sage R&D Day, 2016
Sage's GABA<sub>A</sub> Receptor PAM Design Engine

**Potency/Efficacy**
Diverse library of compounds more potent (*in vitro*) than allopregnanolone

**Selectivity**
GABA<sub>A</sub> receptor α1β2γ2 vs α4β3δ assess selectivity for synaptic vs extrasynaptic receptor subtypes

**DMPK**
Optimizing DMPK for PO delivery & low clearance; optimizing oral bioavailability in rodents and dog
Potential for IV & PO administration
Medicinal Chemistry Approach

- Extensive SAR exploration of C-21 substitutions and chemistry used
- Key intermediates (cis and trans) are 6 steps from a common starting material
- Parallel processing of cis and trans scaffolds

(i) Br₂, CH₃OH ; (ii) Heterocycle, K₂CO₃, DMF or THF

## C-21 Substitutions in the Trans A/B Ring Series

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<th>α₄β₃δ EC₅₀ (nM)</th>
<th>E_max (%)</th>
<th>α₁β₂γ₂ E_max (%)</th>
<th>α₄β₃δ E_max (%)</th>
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Adapted from Martinez Botella et al. *J Med Chem* 2015, 58, 3500.
# C-21 Substitutions in the Cis A/B Ring Series

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<tr>
<th>R</th>
<th>[(^{35})S]TBPS IC(_{50}) (nM)</th>
<th>α1β2γ2</th>
<th>E(_{\text{max}})%</th>
<th>α4β3δ</th>
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<td>EC(_{50}) (nM)</td>
<td>E(_{\text{max}})%</td>
<td>EC(_{50}) (nM)</td>
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DMPK Properties for SGE-516

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<td>Aq. Sol (uM)</td>
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<td>Mouse (Clhep)</td>
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<td>Clearance (L/h/kg)</td>
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<td>Rat %F</td>
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<td>Brain: Plasma ratio</td>
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SGE-516 is a key Sage tool compound for PoC and therapeutic utility

In contrast, diazepam potentiated synaptic receptors \textit{in vitro}

SGE-516 is a key Sage tool compound for PoC and therapeutic utility

Hammond et al \textit{Epilepsy Res} 2017
SGE-516 Demonstrated Broad Preclinical Anticonvulsant Activity

**Anticonvulsant Activity of SGE-516**

**in vitro epileptiform models**
- 0 Mg^{2+} ✓
- 4-AP ✓
- PTZ ✓
- 6 Hz ✓

**in vivo seizure models**
- Corneal Kindling ✓
- Audiogenic in *Fmr1* KO mice ✓
- Scn1a+/- Dravet mouse model ✓

SGE-516 protected against PTZ-induced convulsions in mice

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Hammond et al., 2017 Epilepsy Research

SGE-516 is a key Sage tool compound for PoC and therapeutic utility
Synthesis of SGE-516

1. Pd/C, H₂, HBr, THF (83%)
2. MAD, MeMgBr, THF (90%)
3. EtPPh₃Br, t-BuOK, THF (92%)
4. BH₃, THF
5. 10% NaOH, H₂O₂ (two steps)
6. PCC, CH₂Cl₂ (62%)
7. Br₂, aq. HBr, MeOH (two steps)
8. K₂CO₃, THF (49%)

SGE-516


SGE-516 is a key Sage tool compound for PoC and therapeutic utility.
SGE-516 Opened a Broad Development Opportunity for Other Compounds in a Spectrum of Diseases

Key Sage tool compound for PoC and therapeutic utility

- Orphan Epilepsies
- Pharmacoresistant GABAergic indications

Prolonged survival in the Scn1a+/− Dravet mouse model\(^1\)

Produced anxiolytic-like activity in Vogel Conflict Test model\(^2\)


SGE-516 is a key Sage tool compound for PoC and therapeutic utility
In preclinical studies:
- Highly potent and selective next generation GABA\(_A\) receptor PAM
- PK/PD profile strongly differentiated from 1st Gen NAS
- Oral bioavailability
- Brain penetrant in preclinical studies (B/P > 3)

Martinez Botella et al. J Med Chem 2017, 60, 7810-7819
SAGE-324: Next Generation Oral GABA_A Receptor PAM

Preclinically, SAGE-324 demonstrated:

- Potent, pan-selective modulation of GABA_A receptors
- Oral bioavailability and brain penetrance
Next Generation Asset Positioned for Neurological Conditions

SAGE-324:

• Novel next-generation positive allosteric modulator (PAM) of GABAA receptors
• Chronic dosing: long half-life provided consistent plasma concentrations with minimal daily fluctuations after multiple doses
• Potential therapy for neurological conditions, such as essential tremor, epilepsy and Parkinson’s disease
On Track to Initiate Phase 2 Study in Essential Tremor

- **Essential tremor (ET)** is the most prevalent movement disorder, estimated to affect more than 6M people in the U.S.; up to 1M seek treatment.
- **High unmet need**: 50% of treated patients do not respond or have sub-optimal response to standard of care\(^1\)

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**SAGE GABA PAMS REDUCED TREMOR**

- **zuranolone**
- **brexanolone**

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**SAGE-324 EFFECT OBSERVED AFTER A SINGLE DOSE**

Total upper limb combined score change after SAGE-324 dosing in people with ET as measured by accelerometer

**SAGE-324 was well-tolerated in Phase 1 studies; most common AEs (≥5%) included somnolence, dizziness, and feeling of relaxation**

Source: \(^1\)Louis et al.; Abbreviations: AEs = adverse events

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Summary

- Sage has developed a differentiated approach towards drug development with a focus on translational neuroscience and experimental medicine.
- SGE-516 is a key GABA_A receptor PAM tool compound for proof of concept and therapeutic opportunity.
- Sage is advancing next generation oral GABA_A receptor PAMs into clinical studies.
Acknowledgements

• The Entire Sage Team and special thanks to:

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