Evolution of RAP-219 for the Treatment of Epilepsy

1990s through Early 2000s

An increase in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors is identified in patients with epilepsy. AMPA receptors are found to be absent from cerebellar cells of stargazer mice but are still intact in the forebrain.

2000

Stargazin (γ2) is the first transmembrane AMPA receptor regulatory protein (TARP) discovered to interact with AMPA receptors.

2000s through 2020s

Additional work on receptor-associated proteins (RAPs) reveals that targeting a specific TARP subunit of AMPA receptors (eg, TARPγ8) can selectively affect excitability initiated in the forebrain and therefore can be used to treat certain conditions while also avoiding some adverse events observed with nonselective AMPA receptor inhibitors.

2022

Rapport Pharmaceuticals launches as a biotechnology company.

Purpose for Development

- There is an unmet need for precision target therapies that offer novel mechanisms of action with optimal efficacy and an improved safety profile

AMPA Receptors

- α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are glutamate-gated ion channels that primarily mediate excitatory signaling in the central nervous system (CNS)[1,2]
  - Hippocampal AMPA receptor subunit mRNAs and their proteins were increased in brain tissue of autopsied patients with epilepsy compared with autopsied patients who did not have seizures[3]
  - AMPA receptor inhibition or negative modulation has been studied in various neurological and psychiatric conditions, including epilepsy, pain, and disorders associated with cognitive deficits[4-6]
- Transmembrane AMPA receptor regulatory proteins (TARPs), which include stargazin (γ2), γ3, γ4, and γ8, mediate surface expression of AMPA receptors[7]
- The first TARP discovered to interact with AMPA receptors was stargazin (γ2)[1]
  - Stargazer mutant mice exhibit seizures and cerebellar ataxia, attributed to a lack of functional surface AMPA receptors[1,7-9]
  - However, AMPA receptors in the stargazer mouse forebrain neurons were intact,[7] indicating specificity by isoform to brain regions
- David S. Bredt, MD, PhD (**Image 1**), and Professor Roger A. Nicoll, MD (**Image 2**), recognized that stargazin and related TARPs regulate the synaptic targeting, gating, and pharmacology of AMPA receptors
  - TARPs increase the trafficking of AMPA receptors to both the plasma membrane and synapses[5]
  - TARP isoforms are generally expressed in distinct yet overlapping patterns in the brain[4,10]

Image 1.
David S. Bredt, MD, PhD

Image 2.
Professor Roger A. Nicoll, MD

Image 3.
Steve Paul, MD

Targeting TARPγ8

TARPγ8 Expression

- Broadly expressed in the cortex and amygdala and enriched in the hippocampus[4,7,10,11] (**Figure 1A**)
  - AMPA receptors are selectively depleted in the hippocampus of TARPγ8 knock-out (KO) mice[11]
  - There is minimal TARPγ8 expression in the hindbrain or midbrain

TARPγ8 Function

- Regulates AMPA receptor levels and extrasynaptic surface expression, which plays a key role in long-term potentiation[11]
  - Has long-range effects on the receptors, even though interactions are primarily seen in transmembrane segments and the ligand-binding domain[12]
- AMPA receptor resensitization, a gating characteristic, is also seen with TARPγ8 and contributes to inhibiting neuronal excitability in epilepsy[12,13]
- Nonspecific AMPA receptor antagonists are associated with adverse events (AEs) such as ataxia, motor impairment, dizziness, falling, and sedation[4,14,15]
- Selectively targeting TARPγ8 (**Figure 1B**) may reduce excitatory transmission in the forebrain while improving the therapeutic index seen with nonspecific AMPA receptor antagonists[16-18]

Figure 1A.

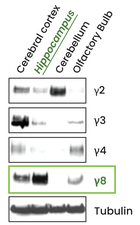
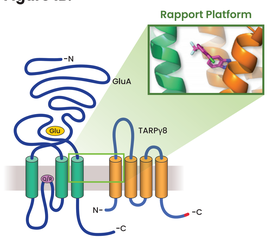


Figure 1B.

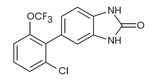


Developing a New Class of Medications

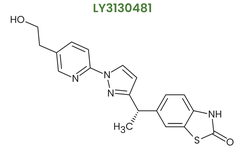
- In 2016, TARPγ8-specific compounds were discovered by Janssen and Lilly (**Figure 2**)[19]
  - JNJ-55511118 (JNJ'118)[4,6]
  - LY3130481 (LLY'481)[16-18]
  - JNJ-56022486[4]
  - All these compounds have broad-ranging anticonvulsant effects without motor side effects because they do not block AMPA signaling in the cerebellum
  - **RAP-219 (formerly known as JNJ-64300912)**

Figure 2.

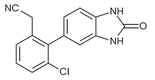
JNJ-55511118



LY3130481



JNJ-56022486



Launch of Rapport Therapeutics with a Focus on Precision Medicine

- Founded by David Bredt, MD, PhD (**Image 1**) and Steve Paul, MD (**Image 3**)
  - Dr. Bredt, co-founder and Chief Scientific Officer, led groundbreaking receptor-associated protein research at Janssen
  - Dr. Paul, co-founder and Chairman of the Board of Directors, has over 40 years of experience in neuroscience and molecular neuropharmacology and CNS drug discovery and development
- Funded through collaboration between Third Rock Ventures and Johnson & Johnson (specifically, Janssen) in February 2022
- A clinical-stage biopharmaceutical company focused on the discovery and development of a portfolio of precious small molecule product candidates that we believe have the potential to transform the standard of care of many CNS disorders

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Evolution of RAP-219 for the Treatment of Epilepsy

2023-2024

Single ascending dose (SAD) and multiple ascending dose (MAD) studies initiated. NeuroPace partnership established. Phase 2 proof-of-concept (POC) study in focal onset seizures initiated.

Looking Forward

Advancing a pipeline of therapeutic programs with the goal of bringing new medications to patients living with CNS disorders.

Focal Onset Seizures (FOS)

- Over 30% of people with epilepsy experience drug-resistant epilepsy (DRE) despite the existence of multiple treatment options
  - Probability of achieving seizure freedom decreases with each unsuccessful treatment[1]
  - Nonspecific AMPA receptor antagonists are associated with adverse events (AEs) such as ataxia, motor impairment, dizziness, falling, and sedation[2-4]

Preclinical Efficacy of NAMs Targeting TARPγ8

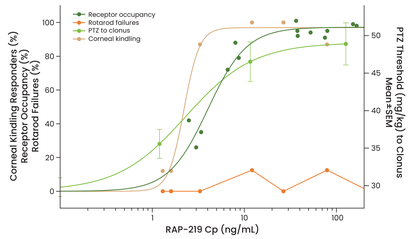
- Targeting RAPs provides cell-type and/or neuroanatomical specificity and allows optimal efficacy with a tolerable safety profile
- **RAP-219 is an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor negative allosteric modulator selective for TARPγ8**
- TARPγ8-specific compounds have shown robust efficacy across a broad array of preclinical focal and generalized seizure models (**Table 1**)
  - RAP-219 specifically has demonstrated efficacy in pentylenetetrazol (PTZ) and corneal kindling (CK) models without motoric impairment on a rotarod (**Table 1, Figure 1**)
  - In mice, seizures were prevented following oral administration of RAP-219 at a receptor occupancy of 70%
  - RAP-219 has a wide therapeutic index, unlike other antiseizure medications (ASMs) that have more narrow therapeutic indexes (**Figure 2**)

Table 1. TARPγ8 Compounds in Preclinical Pharmacology

Model or Test	Validated	γ8-TARP Compounds Tested
PTZ – mouse	✓	**RAP-219**, JNJ'118, RAP-482, and LLY'481 active
Maximal electroshock – mouse	✗	RAP-219, JNJ'118, RAP-482, and LLY'481 not active
Corneal kindling – mouse	✓	**RAP-219**, JNJ'118, RAP-482, and LLY'481 active
Amygdala kindling – mouse	✓	JNJ'118, RAP-482, and LLY'481 active | RAP-219 not tested
Hippocampal kindling – mouse	✓	LLY'481 active | JNJ compounds not tested
Frings audiogenic seizure – mouse	✓	LLY'481 active | JNJ compounds not tested
GAERS absence epilepsy – rat	✓	LLY'481 active | JNJ compounds not tested
Rotarod	✓	**RAP-219**, JNJ '118, RAP-482, and LLY'481 = wide safety margin

GAERS – genetic absence epilepsy rats from Strasbourg; **JNJ** – Johnson & Johnson; **PTZ** – pentylenetetrazol; **TARP** – transmembrane AMPA receptor regulatory protein.

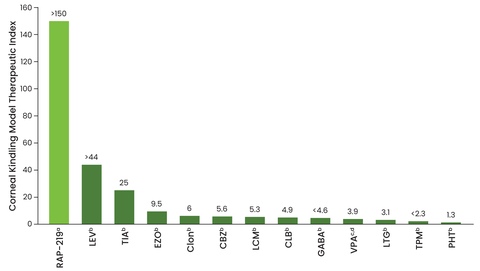
Figure 1. RAP-219 Receptor Occupancy, Antiseizure Efficacy, and Rotarod Failures as Functions of Plasma Concentration



Receptor occupancy as a function of plasma concentration in rat at t=4h was used as a surrogate for this analysis, as potency in mouse vs rat was nearly identical (mouse pIC_{50}=9.8; rat pIC_{50}=9.9). PTZ threshold, corneal kindling, and rotarod were assessed in mouse.

PTZ – pentylenetetrazol.

Figure 2. Therapeutic Indices of RAP-219 and Commonly Used Antiseizure Medications



[a]Data on file, Rapport Therapeutics[5]; [b]https://panache.ninds.nih.gov/[6]; [c]Metcalf CS, et al. *Epilepsia* 2017;58(6):1073-1084[7]; [d]Rowley NM, White HS. *Epilepsy Res.* 2010;92(2–3):163-9[8].

CBZ – carbamazepine; **CLB** – clobazam; **Clon** – clonazepam; **EZO** – ezogabine; **GABA** – gabapentin; **LCM** – lacosamide; **LTG** – lamotrigine; **LEV** – levetiracetam; **PHT** – phenytoin; **TIA** – tiagabine; **TPM** – topiramate; **VPA** – valproate.

RAP-219 Clinical Program

- Phase 1 studies characterizing single and multiple dose PK/tolerability
- Results from the Phase 1 trials conducted have revealed that RAP-219 is associated with:
  - Estimated >80% occupancy bioavailability, allowing oral administration
  - Long terminal half-life (8-14 days)
  - >95% protein binding
  - Metabolism via UGT1A4
    - Low risk of drug-drug interactions with other ASMs metabolized by CYP450 enzymes
  - No abnormalities observed in vital signs, laboratory values, or electrocardiograms in SAD and MAD studies
  - In a Phase 1 MAD study, target exposures were achieved without sedation or motoric impairment
- The Phase 2A study of RAP-219 for the treatment of medically refractory FOS uses a novel POC design in partnership with NeuroPace (NCT06377930; **Figure 3**)
  - The RNS POC study paradigm offers new methodologies and outcome measures while also reducing timelines and yielding scientifically valid results
  - Using quantitative intracranial EEG (iEEG) biomarker outputs from implanted responsive neurostimulators (RNS® System, NeuroPace, Inc.) as a surrogate biomarker for reduction in clinical seizure frequency, the aim is to establish POC for RAP-219 in the treatment of medically refractory FOS
- The RAP-219 program leaders and Rapport Therapeutics Pipeline are displayed in **Images 1-4** and **Figure 4**, respectively

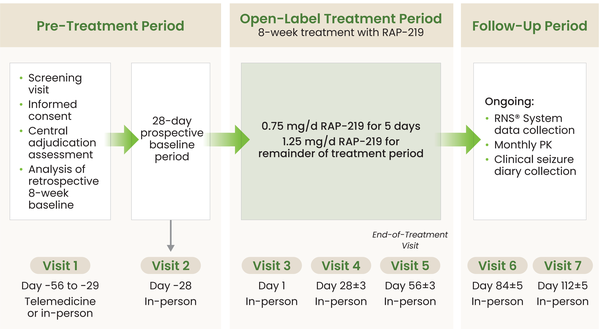
Image 1.
Swamy Yeleswaram, PhD
Chief Development Officer, Rapport Therapeutics

Image 2.
Brad Galer, MD
Chief Medical Officer, Rapport Therapeutics

Image 3.
William Motley, MD
RAP-219 Program Lead, Rapport Therapeutics

Image 4.
Martha Morrell, MD
Chief Medical Officer, NeuroPace

Figure 3. Phase 2A Proof-of-Concept (POC) Study Design



PK – pharmacokinetic; **RNS®** – responsive neurostimulator.

Figure 4. Rapport Therapeutics Pipeline[9]

Category	Program	Discovery	Preclinical	Phase 1	Phase 2	Phase3
TARPγ8 AMPAR programs	RAP-219 *focal epilepsy*			■		
	RAP-219 *peripheral neuropathic pain**			■		
	RAP-219 *bipolar disorder*			■		
nAChR discovery programs	α6 *chronic pain*		■			
	α9α10 *hearing disorders*		■			

*Subject to resolution of clinical hold with the FDA.

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