BRIGHT MINDS

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5-HT_{2C} Agonism: Multiple Animal Models Supporting the Efficacy in Developmental and Epileptic Encephalopathy (DEE) Indications

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2025 AES ANNUAL MEETING
DECEMBER 5-9 • ATLANTA

Background

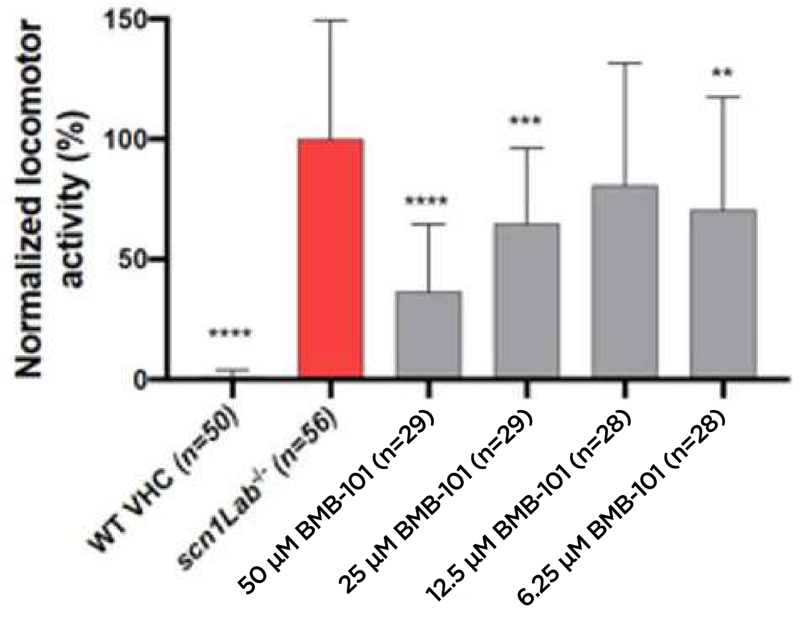
- The 5-HT_{2C} receptor (serotonin 2C receptor), a G protein-coupled receptor has emerged as a potential target for epilepsy treatment due to its role in modulating neurotransmitter release and neuronal excitability
- Traditional 5-HT_{2C} agonists can lead to receptor desensitization, through receptor internalization due to β-arrestin recruitment, reducing long-term efficacy[1]
- Efficacy in preclinical models of Developmental and Epileptic Encephalopathies (DEEs) has been demonstrated for fenfluramine, lorcaserin, and bexicaserin[2]
- Similar efficacy can be achieved with the 5-HT_{2C} G-protein biased agonist BMB 101:
  - Dose-dependent reductions of epileptiform activity and locomotor activity in the Zebrafish model of Dravet Syndrome[2,3] have been demonstrated
  - In rodents (rats and mice) our G-protein biased agonist was tested in the acute maximal electroshock seizure (MES) threshold model, evaluating the seizure threshold and the anticonvulsant properties

Results

scn1Lab Zebrafish model (Dravet Syndrome model)

- BMB-101 reduced locomotor activity (Figure 1a) and reduced the cumulative duration of epileptiform events in the brain of Zebrafish larvae (Figure 1b)
- The data provides clear evidence that BMB-101 has a therapeutic effect on both the number of and duration of the abnormal brain activities in scn1Lab Zebrafish resulting in pronounced antiseizure activity

A



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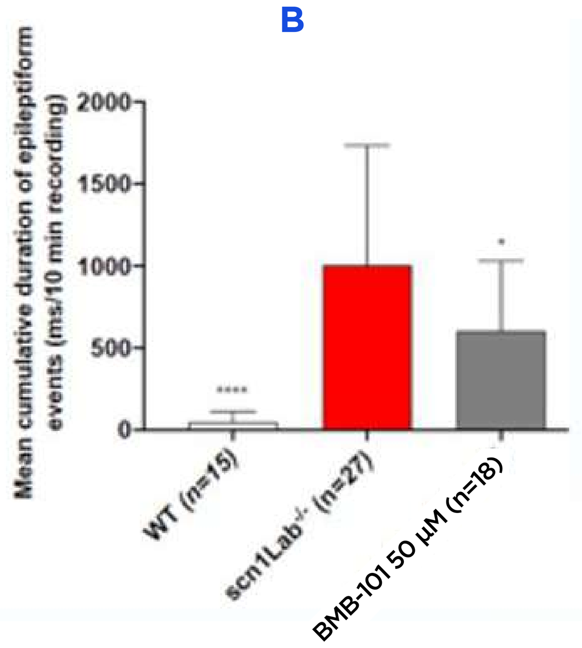

Protection against electroshock-induced seizures in mice and rats

- In the National Institutes of Health (NIH) Epilepsy Therapy Screening Program (ETSP), the BMB-101 analog (JJ42) was tested intraperitoneally in the rat MES model
- In the initial screening assay, 30 and 50 mg/kg of the test drug provided significant protection against MES-induced generalized seizures in rats
- Toxicity was not observed at any doses
- JJ42 at concentrations of 3, 10, and 30 mg/kg did not cause any motor impairments on rotarod, and no mortality at 72 hours was observed

Table 1. BMB-101 analog (JJ42) in the rat MES model

Dose	Test	0.25 h	1 h
		Protected/total	
10 mg/kg	MES	0/4	0/4
30 mg/kg	MES	3/4	0/4
50 mg/kg	MES	4/4	4/4
	N=4 for each dose		
10 mg/kg	TOX	0	0
30 mg/kg	TOX	0	0
50 mg/kg	TOX	0	0

- JJ42 was further tested in the mice and rat MES model and produced dose-dependent anti-seizure activity with ED_{50} of 23.4 mg/kg and 9.86 mg/kg, respectively
- Note that JJ42 has lower 5-HT_{2C} efficacy and potency in rat receptors compared to human, and is also rapidly metabolized in rats, leading to an underestimation of efficacy in animal models

Table 2. MES model: Antiseizure activity in rats after IP administration (0.5-hour timepoint)

Dose	Protection (N=8)
5 mg/kg	1/8
15 mg/kg	6/8
30 mg/kg	8/8

Table 3. MES model: Antiseizure activity in male mice after IP administration (0.5-hour timepoint)

Dose	Tolerability (N=8)	Protection (N=8)
15 mg/kg	100%	1/8
22.5 mg/kg	100%	3/8
30 mg/kg	100%	7/8
45 mg/kg	100%	8/8

Conclusions

- The seizure reductions observed with BMB-101 in the Zebrafish model of Dravet syndrome and with JJ42 in both the mouse and rat MES model support that the anti-epileptic drug effect is mediated through G-protein signaling.
- The observed effect is at least comparable to those seen with lorcaserin and fenfluramine
- Better tolerability was observed with BMB-101, allowing exploration of higher target occupancy, yielding better seizure management in Zebrafish and rodent models

Acknowledgements

The preclinical research work on JJ42 was completed by the United States NIH Epilepsy Treatment Screening Program.

Additional preclinical and clinical research with BMB-101 was conducted by Bright Minds Biosciences, Inc.

References

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