BMB-101 and Biased 5-HT$_{2C}$ Agonism: A Novel Approach for Sustained Epilepsy Management

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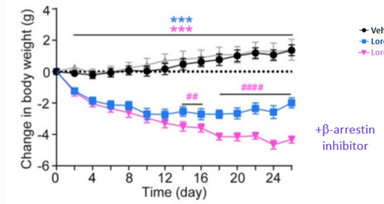
Introduction

- The 5-HT$_{2C}$ receptor (serotonin 2C receptor), a G protein-coupled receptor (GPCR), 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** (β-arr) recruitment, reducing long-term efficacy (Rankovic et al. 2016).
- Lorcaserin was found to highly desensitize 5-HT$_2$ receptors, more than 5-HT, possibly due to a "super agonist" action at recruiting β-arrestin (Felsing et al. 2019).
- Reduced fenfluramine and lorcaserin **long-term efficacy** as anti-obesity drugs has been proposed to be caused by **β-arrestin recruitment at 5-HT2CRs, leading to desensitization of the receptors and clinical tolerance** (He et al. 2021).

About BMB-101

- **A novel scaffold 5-HT$_{2C}$ agonist** explicitly designed for chronic treatment of neurological disorders where tolerance and drug resistance are common issues.
- **Biased agonism / Functional selectivity**: BMB-101 works exclusively via the Gq-protein signaling pathway and avoids beta-arrestin activation. This is crucial to minimize the risk of receptor desensitization and tolerance development.
- **Validated in preclinical models**: BMB-101 has demonstrated efficacy in animal models of Dravet Syndrome and several models of generalized seizures
- **A novel mechanism**, anti-epileptic drug designed to provide sustained seizure relief in hard-to-treat patient populations

Lessons from Lorcaserin



Deactivation of β-arrestin produces a superior and sustained effect in long term Lorcaserin use (in vivo study)

Adapted from He et al. 2021

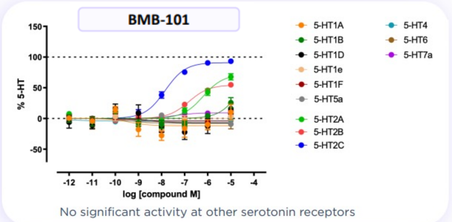
BMB-101: highly selective 5-HT$_{2C}$ receptor agonist, not recruiting β-arr

- **BMB-101 is a full 5-HT$_{2C}$ agonist** with minimal activity at 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors, thus not possessing liabilities linked to psychedelic and cardiotoxic effects, respectively.
- BMB-101 shows a **great preference for Gq dissociation** at 5-HT$_{2C}$ vs. β-arr2 recruitment (β-arr2: Emax < 20%, EC$_{50}$= not calculable), contrarily to Norfenfluramine and Lorcaserin that recruit both Gq and β-arr.

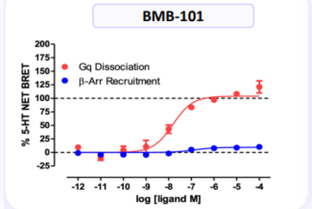
Absolute EC$_{50}$ (nM)

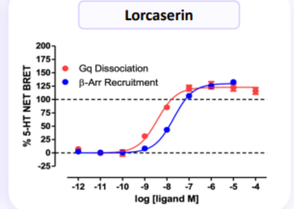
Compound	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$
BMB-101	2280	>10000	16.2
Nor-Fenfluramine	82.8	11.6	2.5
Lorcaserin	50.1	67.4	2.4
Bexicaserin	>10000	>10000	120

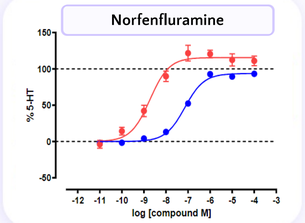
Internal data for BMB-101, fenfluramine, lorcaserin. Bexicaserin data from Longboard corporate deck



No significant activity at other serotonin receptors







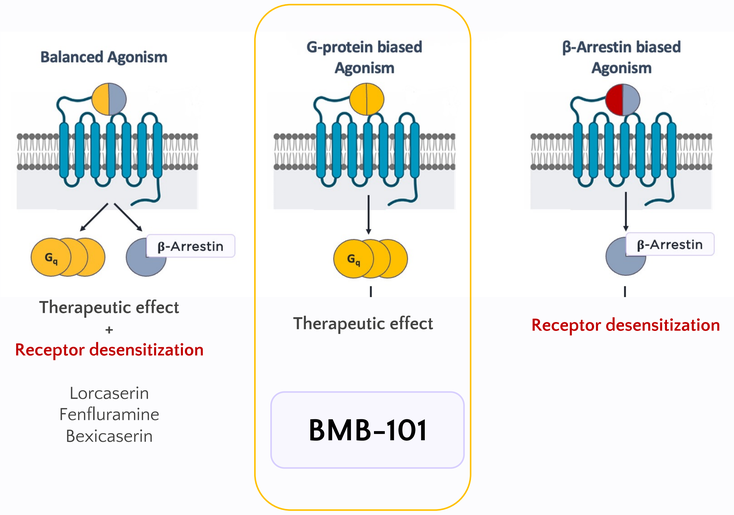
In vitro Pharmacology (John McCorvy group): Effector engagement induced by human 5-HT receptors was measured using Gq dissociation as measured by bioluminescence resonance energy transfer (BRET). Emax was defined relative to serotonin (5-HT).

Innovative approach: Biased-agonism

G protein biased agonists (or functionally selective agonists) - new generation of medications, with potentially improved efficacy, and/or less tolerance.

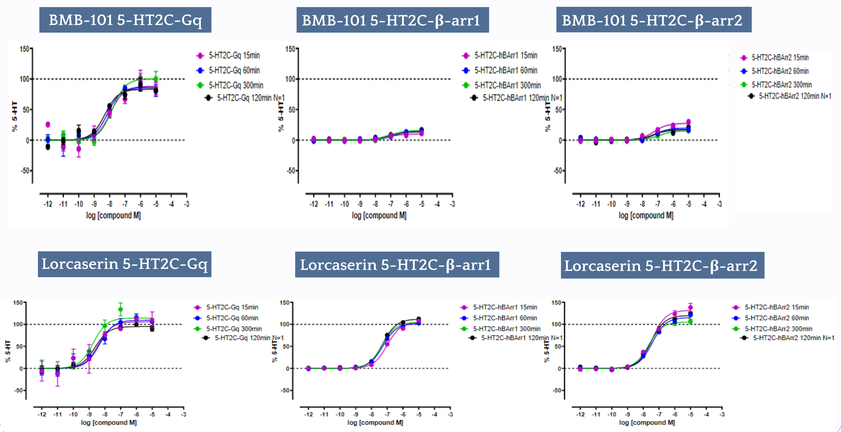
Examples of biased GPCR agonists with improved long-term efficacy:
- Tirzepatide - G-protein biased GLP1 agonist for weight management (developed by Eli Lilly)
- Oliceridine – G-protein biased μ-opioid receptor for severe pain (developed by Trevena)
- CT-868 – G-protein biased GLP1 agonist (developed by Carmot, acquired by Roche)

BMB-101 is the only biased 5-HT2C agonist in development



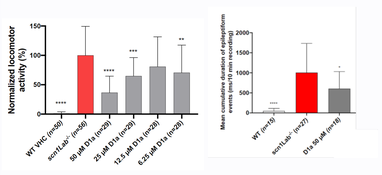
Biased agonism: BMB-101 does not recruit any β-arr subtype

BMB-101 was subsequently tested for recruitment of **b-arrestin subtypes** (β-arr1 and β-arr2) and compared to Lorcaserin. BMB-101 exhibits very weak partial agonism of β-arr1 and β-arr2 recruitment (βarr1: Emax =12.9%; βarr2: Emax = 20.8%) compared to Gq dissociation. Lorcaserin, on the other hand, is superagonist at β-arr1 and β-arr2 (βarr1: Emax = 100.3%; βarr2 Emax = 107.4%). BMB-101 shows again a greater preference for Gq dissociation agonist activity, contrarily to Lorcaserin, thus **demonstrating Gq-biased agonism effects robust across time (15, 60, 120 and 300 min)**.



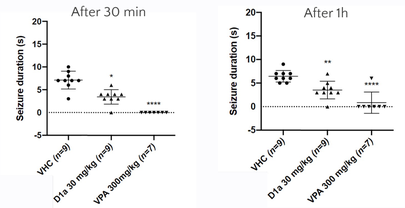
Biased agonists: *in vivo* efficacy

scn1lab **zebrafish model (Dravet Syndrome model)**



Epileptiform activity as duration and frequency of epileptiform events for scn1Lab-/- treated larvae with BMB-101. Statistically defined outliers were removed. BMB-101 is coded as D1a

Mouse 6-Hz (44 mA) (psychomotor seizure model)



Drug-resistant psychomotor seizures were induced 30 min/1 h after i.p. injection of vehicle (VHC), positive control valproate (VPA) and BMB-101 (coded as D1a)

Proprietary biased agonists developed by Bright Minds Bio (BMB-101 and JJ42) demonstrate efficacy in other preclinical in vivo models of epilepsy and impulsivity related disorders:
- Binge eating: -50% reduction of binge eating episodes, as well as noted weight loss
- Substance Use Disorder: -60% reduction of fentanyl self-administration
- Maximum Electroshock model – presented at Society for Neuroscience conference *(Vasilkevich, A, et al, Selective 5-HT2C Agonists for the Treatment of Rare Epileptic Disorders, presented at SfN Conference 2024, October 5-9, Chicago)*

Conclusions

- βArr activation is associated with steric hindrance of further 5-HT$_{2C}$ Gq activation, 5-HT$_{2C}$ receptor internalization and impeding further stimuli of the 5-HT$_{2C}$ receptor. This mechanism has been proposed to cause long-term inefficacy of Lorcaserin and Fenfluramine.
- **BMB-101 is the only Gq-biased 5-HT$_{2CR}$ selective agonist in clinical development** (phase II initiated in Q4 2024), only targeting one of the GPCR pathways without βArr1 and 2 recruitment, thus suggesting lack of tolerance in humans
- BMB-101 demonstrated anti-seizure activity in preclinical models and is now into a Phase II trial on developmental and epileptic encephalopathy (DEE) and absence epilepsy.

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