53. SPR-Inhibitors in the field of Neuropathic Pain

(Lead Discovery Center)

5TH KDDF GLOBAL C&D TECH FAIR

Asset Overview

Product Type	Small molecule
Disease Area	CNS Diseases
Indication	Pain, IBD
Current Stage	Lead optimization
Target	Nociceptive signaling
MoA	Tetrahydrobiopterin (BH4) critically involved in nociceptive signaling
Brief Description	• Tetrahydrobiopterin (BH4) is an enzyme cofactor for various aromatic amino acid hydroxylases, including phenylalanine, tyrosine and tryptophan hydroxylases, as well as being an important cofactor for other enzymes such as the nitric oxide synthases (inducible NOS (iNOS), endothelial NOS (eNOS), and neuronal NOS (nNOS)), and alkylglycerol monooxygenase. As such, BH4 is involved in regulating production of various neurotransmitters (e.g., serotonin and dopamine) and nitric oxide. Deficiencies in BH4 are associated with deficiencies in neurotransmitters including serotonin and dopamine. Reduced BH4 production is also associated with reduced pain sensitivity after injury • Basic principle: Tetrahydrobiopterin (BH4) critically involved in nociceptive signaling ➢ humans: gene-variants of GTP cyclohydrolase 1 (rate-limiting step in BH4 synthesis) effectively modulates pain ➢ (i) BH4 levels increased in injured sensory neurons, (ii) BH4 induces nitric oxide (NO) biosynthesis, (iii) NO important transmitter involved in nociceptive processes, (iv) blockade of sepiapterin reductase (SPR) effectively blocks BH4 production (in vitro & in vivo validation)
Intellectual Property	WO2017059191A1
Publication	-
Inventors	Mark Joseph Tebbe, Holly Victoria ATTON, Craig AVERY, Steven Mark Bromidge, Mark KERRY, Adrian Kotei Kotey, Nathaniel J. MONCK, Mirco Meniconi, Mark Peter Ridgill, Heather Tye, Eddine Saiah, Kai Peter JOHNSSON, Katarzyna Irena GORSKA, Hairuo Peng, John Michael Mccall

Highlights

- Access to highly potent SPR inhibitors (lead optimization stage and compound series comprising ~2.000 cpds)
- In-depth characterization of small selection of compounds: PK/PD, ADME, toxicology (mouse, rat, limited dog and NHP data)
- Current activities & next steps
- Identification of peripherally restricted frontrunner leads from PK dog-study for candidate nomination experiments (tolerability, MTD, RDT, allometric scaling, etc.)
- SPR (BH4)
- In vivo efficacy (Proof of concept) with next generation SPR inhibitors demonstrated in SNI and post-operative pain models

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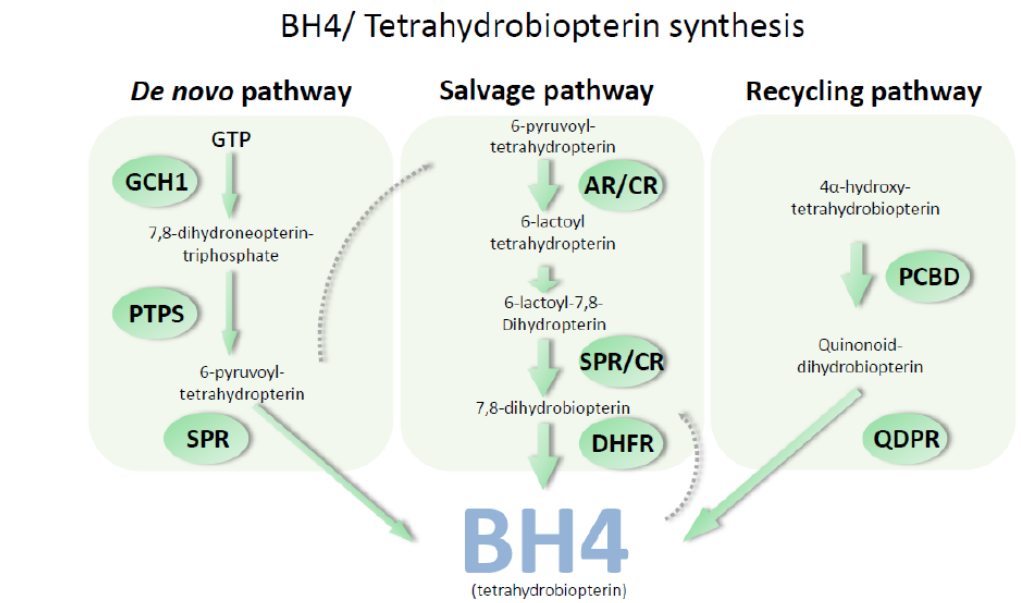
Key Data

BH4/Tetrahydrobiopterin synthesis



GCH1: GTP cyclohydrolase I

PTPS: Pyruvoyl tetrahydrobiopterin synthase

SPR: sepiapterin reductase

AR: Aldose reductase

CR: Carbonyl reductase

DHFR: Dihydrofolate reductase

PCBD: Pterin-carbinolamine dehydratase

QDPR: quinoid dihydropteridine reductase