295 BH4

Asset Overview

Product Type	Small Molecule
Indication	Oncology
Current Stage	Hit
Target(MoA)	Sepiapterin Reductase Inhibitor
Brief Description	Tetrahydrobiopterin (BH4) is an enzyme cofactor for various aromatic amino acid hydroxylases and it is involved in production of various neurotransmitters and nitric oxide. BH4 is biosynthesized through multiple steps and sepiapterin reductase is critical for the final biosynthesis step of BH4. Inhibition of BH4 biosynthesis via sepiapterin reductase inhibition prevents T cell proliferation and T cell-induced autoimmunity.
Organization	Lead Discovery Center

Differentiation

□ **Genetic regulators and environmental stimuli modulate T cell activation in autoimmunity and cancer**

- The enzyme co-factor tetrahydrobiopterin (BH4) is involved in the production of monoamine neurotransmitters, the generation of nitric oxide, and pain
- Link between these processes, identifying a fundamental role for BH4 in T cell biology. : genetic inactivation of GTP cyclohydrolase 1 (GCH1, the rate-limiting enzyme in the synthesis of BH4) and inhibition of sepiapterin reductase (the terminal enzyme in the synthetic pathway for BH4) severely impair the proliferation of mature mouse and human T cells
- BH4 production in activated T cells is linked to alterations in iron metabolism and mitochondrial bioenergetics. In vivo blockade of BH4 synthesis abrogates T-cell-mediated autoimmunity and allergic inflammation, and enhancing BH4 levels through GCH1 overexpression augments responses by CD4- and CD8-expressing T cells, increasing their antitumour activity in vivo
- Administration of BH4 to mice markedly reduces tumour growth and expands the population of intratumoral effector T cells. Kynurenine—a tryptophan metabolite that blocks antitumour immunity—inhibits T cell proliferation in a manner that can be rescued by BH4
- The development of a potent SPR antagonist for possible clinical use. GCH1, SPR and their downstream metabolite BH4 as critical regulators of T cell biology that can be readily manipulated to either block autoimmunity or enhance anticancer immunity

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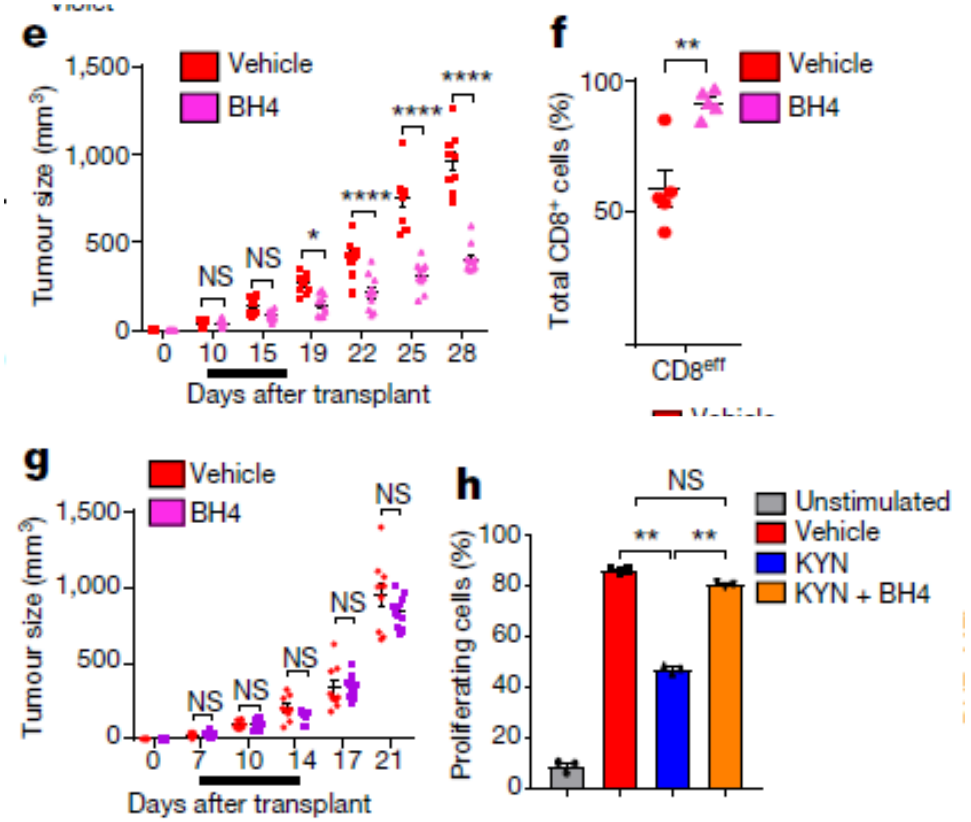
Key Data

Enhanced BH4 production results in enhanced T cell proliferation and anticancer immunity



Treatment of mice carrying established E0771-derived mammary tumours with BH4 slowed the growth of the tumours (Fig. 4e). Tumours in BH4-treated mice displayed increased frequencies of activated effector CD4+ and CD8+ cells among the infiltrating T cells, compared with vehicle-treated mice (Fig. 4f and Extended Data Fig. 10d). BH4 treatment in Rag2−/− hosts had no effect on breast-cancer growth, confirming that the effect of BH4 is via effects on the adaptive immune system (Fig. 4g).

Intellectual Property

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Contact Information

Contact Person	Sven Zimmer
Email	zimmer@lead-discovery.de
URL	https://www.lead-discovery.de/en/strategy/