(SD2020-014) Biosynthetic Production Of L-4-Chlorokynurenine

Tech ID: 31850 / UC Case 2020-014-0

BACKGROUND

The non-proteinogenic amino acid l-4-chlorokynurenine (l-4-Cl-Kyn) is a next-generation, fast-acting oral prodrug for the treatment of major depressive disorder. Additional studies report that this drug candidate is effective in animal models for the treatment of neuropathic pain, epilepsy, and Huntington's disease. After active transport across the blood–brain barrier, it is enzymatically converted into the active agent 7-chlorokynurenic acid, which is a highly selective competitive antagonist of the *N*-methyl-d-aspartic acid (NMDA) receptor.

Suicide is 2-7x higher in Veterans than non-veterans, and may be related to brain kynurenine pathway (KP) dysregulation and NMDA receptor (NMDAR) hyperactivation. L-4-Chlorokynurenine (L-4-Cl-Kyn) is a neuropharmaceutical drug candidate that is in development for the treatment of major depressive disorder (Double-Blind, Placebo-Controlled, Phase 2 Trial to Test Efficacy and Safety of AV-101 (L-4-chlorokynurenine) as Adjunct to Current Antidepressant Therapy in Patients With Major Depressive Disorder (the ELEVATE Study)).

TECHNOLOGY DESCRIPTION

Researchers from UC San Diego discovered four genes from the taromycin-producing marine bacterium Saccharomonospora sp. CNQ-490 and showed in the laboratory that their encoded enzymes convert L-tryptophan to L-4-chlorokynrenine. This work, therefore, opens up an opportunity for cost-effective and environmentally friendly bioproduction of this medicinaly critical and commercially important molecule. Importantly, due to the rare ability L-4-chlorokynrenine to cross the blood-brain barrier and existence of gut-brain axis, it is anticipated that discovered bacteria-derived genes will initiate development of microbiome-based therapeutic (engineered probiotic strain) as a promising alternative treatment of neurological disorders.

The inventors showed that they could produce L-4-chlorokynurenine in a single reaction vessel, which they consider proof for the claims they make to biologically produce L-4-chlorokynurenine. And the researchers anticipate that their discovery may be further developed and applied for the following purposes (see below).

APPLICATIONS

Developing “living medicine” - probiotic strain capable to produce L-4-chlorokynurenine inside the gut of patients. This is a novel approach for alternative treatment options that holds promise for future use in clinic. Availability of L-4-chlorokynurenine biosynthetic genes presents a unique opportunity for engineering of such strain. Importantly, majority of tryptophan metabolism takes place in the digestive tract where absorption of metabolic products occurs, and it was shown that L-4-chlorokynurenine is easily transported across the blood-brain barrier. Therefore, the discovered genes can be applied to generate live bacterial therapies for neurological disorders.

The newly described biosynthetic enzymes can be engineered and applied for the chemoenzymatic synthesis of kynurenine analogues (e.g., isotope-labeled or with substituents on aromatic part of the molecule).

Biosynthetic production of L-4-chlorokynurenine (by bacterial fermentation).

ADVANTAGES

The newly described biosynthetic enzymes can be engineered and applied for the chemoenzymatic synthesis of kynurenine analogues (e.g., isotope-labeled or with substituents on aromatic part of the molecule). Biosynthetic production of L-4-chlorokynurenine (by bacterial fermentation) would allow engineered expression of the discovered genes in a suitable host which will allow robust, cost-efficient, and green production of L-4-chlorokynurenine.

STATE OF DEVELOPMENT

The researchers have proved *in vivo* and *in vitro* functions of the biosynthetic enzymes involved in this biotransforation and were able to reconstitute *in vitro* one-pot convertion of L-tryptophan (as well as its various analogues) to L-4-chlorokynurenine.

INTELLECTUAL PROPERTY INFO

The invention is patent-pending and is available for licensing and collaborations.

RELATED MATERIALS

► Luhavaya H, Sigrist R, Chekan JR, McKinnie SMK, Moore BS. Biosynthesis of l-4-Chlorokynurenine, an Antidepressant Prodrug and a Non-Proteinogenic Amino Acid Found in Lipopeptide Antibiotics. Angew Chem Int Ed Engl. 2019 Jun 17;58(25):8394-8399. doi: 10.1002/anie.201901571. Epub 2019 May 13 - 05/13/2019

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OTHER INFORMATION

KEYWORDS

NMDA receptor, N-methyl-D-aspartate receptor, depression, antidepressant prodrug, NMDAR, chemoenzymatic synthesis, biosynthesis, chlorokynurenine, biocatalysis

CATEGORIZED AS

- **Biotechnology**
  - Industrial/ Energy
- **Materials & Chemicals**
  - Biological
- **Medical**
  - Other
- **Engineering**
  - Other

RELATED CASES

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PATENT STATUS

Patent Pending

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