Human Butyrylcholinesterase and Acetylcholinesterase Based Catalytic Bioscavengers of Organophosphates

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BACKGROUND

Exposure to organophosphates (OP) from both pesticides and nerve agents leads to inhibition of acetylcholinesterase (AChE), resulting in a build-up of acetylcholine in the body, and potentially death. The only OP stoichiometric bioscavenger in use today is butyrylcholinesterase (hBChE). Human butylcholinesterase (hBChE) specifically and efficiently captures offending OP molecules in the circulation of exposed individuals, sequestering the OP as an inactive conjugate in the plasma.

TECHNOLOGY DESCRIPTION

Researchers at UCSD and The Scripps Research Institute have designed small reactivator molecules that reactivate human butyrylcholinesterase (hBChE) inhibited by OPs in plasma, lungs and intestine of OP exposed individuals in order for single hBChE molecule to repeatedly, covalently, bind and degrade multiple OP molecules effectively depleting OP from the circulation. These are novel antidotes, structurally unrelated to currently used acetylcholinesterase (AChE) reactivators.

They also designed another group of small reactivator molecules to pair with particular mutant hAChE to interact effectively with OP- mutant hAChE inhibited by OPs in order for single mutant hAChE molecule to repeatedly, covalently bind and degrade multiple OP molecules, thus effectively depleting the OP from the circulation. One pair is designed to increase hAChE's efficacy against a wider spectrum of OP toxicants including those prone to dealkylation (aging). The other pair is specifically designed to deplete the tabun OP from circulation, and to reactivate tabun-inhibited AChE.

APPLICATIONS

• Treatment of OP-poisoning from accidental and intentional exposure to insecticides. Organophosphates are widely used in agriculture in the US and worldwide.

• A universal antidote to nerve agents as countermeasures to chemical terrorism.

• An antidote to tabun OP. The effective, catalytic OP bioscavenger system for tabun exposure has not been described before.

STATE OF DEVELOPMENT

Proof of principle demonstrated *in vitro*, *in vivo* in mice and *ex vivo* with human blood.

RELATED MATERIALS

▶ Radic Z, Dale T, Kovarik Z, Berend S, Garcia E, Zhang L, Amitai G, Green C, Radic B, Duggan BM, Ajami D, Rebek J, Taylor P. Catalytic detoxification of nerve agent and pesticide organophosphates by butyrylcholinesterase assisted with non-pyridinium oximes. Biochem J. 2013 Feb 15;450(1):231-42. doi: 10.1042/BJ20121612. - 02/15/2013

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	10,172,831	01/08/2019	2014-091
United States Of America	Published Application	19-0337911	11/07/2019	2012-317
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OTHER INFORMATION

KEYWORDS

organophosphate poisoning, nerve agent, OP-poisoning antidote, achetylcholinesterase, butyrylcholinesterase, AChE, hAChE, hBChE, tabun, aging nerve agent

CATEGORIZED AS

- **Medical**
  - Other
  - Therapeutics
- **Security and Defense**
  - Food and Environment
  - Other

RELATED CASES

2014-091-0, 2012-317-0

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