Design, Synthesis and Biological Evaluation of Innovative Broad-Spectrum Reactivators of neurotoxic organophosphorus inhibited human CholinEsterase

Background

Organophosphorus nerve agents (**OPNA**) have experienced a resurgence recently with their large-scale use against civilians during the attacks in Syria (2013, 2017), the assassination of Kim Jong-nam in Malaysia (2017), the poisoning of Sergei and Yulia Skripal in the UK (2018) and Alexeï Navalny in Russia (2020), strongly renewing the importance of ***antidotes development*** against these lethal synthetic compounds.[1] Organophosphorus pesticides (OPP) used for agricultural purposes are also regarded as a potential threat in a terrorist context. According to the World Health Organization (WHO), 3 million cases of OPP poisoning occur in the world, causing 200,000 deaths per year in developing countries. Due to their ease of production, organophosphorus compounds (OP) have been developed and stock-piled on a large scale, increasing the population's chemical risk. Recently, the emergence of Novichok as the fourth generation OPNA and its use against civilians (2018, 2020) have re-emphasized the need for ***broad-spectrum medical countermeasures (MCM)*** against these agents to ensure the global safety of all civilians in the world, preventing nerve agent intoxications.

The high toxicity of OPNA is caused by covalent binding to a serine hydroxyl residue at the active site of the pivotal acetylcholinesterase, key enzyme of the cholinergic neurotransmission system.

Subsequent accumulation of the acetylcholine (ACh) neurotransmitter and overstimulation of muscarinic and nicotinic receptors results in the development of multiple characteristic clinical symptoms, such as miosis, muscle spasm, convulsion, paralysis, breathing failure, and finally death due to respiratory arrest.

Recently, our research group discovered and patented the first (i) broad spectrum hybrid reactivators, and the first fluoro-hybrid reactivators of inhibited cholinesterases, opening a new era in this domain of investigation. Expanding the scope of this new family of original molecules is crucial for the development of the new generation antidotes.

The aims of this Thesis Research Project are to design, synthesize and evaluate biologically novel multifunctional AChE reactivators on mice and zebra fish model, with high blood brain barrier (BBB) *in vivo* penetration ability, low hepatotoxicity and with broad reactivation spectrum capabilities. The work will be realized at ICPEES and between collaborating groups, including Institut de Recherche Biomédicale des Armées (**IRBA**), the Institute de Biologie Structurale of Grenoble (**CEA**). Candidates should expect to experience exciting scientific adventures within an interdisciplinary worldwide research environment, at the crossroads of organic and bio-organic chemistry, biology and structural biology.

HOW TO APPLY: The candidate should have a **MASTER** in synthetic **Organic Chemistry** or in **Chemistry and Biology** with a strong background in organic synthesis. Strong motivation for research in a competitive area is expected. Applications (*CV +motivation letter as well as 3 references*) should be sent **by e-mail** to: rachid.baati@unistra.fr.