WG 1 (Chemical, Biological, Radiological and Nuclear materials)

Computational Identification of Repurposed Combinatorial Treatments for CBRN Threats: A Text Mining Approach to Evidence-Based Countermeasure Development

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This study presents a novel computational approach for identifying repurposing opportunities of existing treatments against chemical, biological, radiological, and nuclear (CBRN) threats. Utilizing advanced text mining methodologies through the SPIKE platform for extractive search, CoreMine Medical, Embase, and Clinical Queries, we developed a structured framework for mapping hazardous agents to potential therapeutic interventions. Our approach involved constructing specialized threat categories and cross-referencing them with comprehensive drug databases to identify evidence-based connections. To enhance precision, we employed contextual keyword enhancement and AI-driven (LLM) validation strategies, effectively filtering irrelevant associations. The methodology can identify promising treatment candidates for toxic industrial gases, nerve agents, opioid toxicity, and radiation exposure, with specific emphasis on combinatorial interventions. This systematic approach bridges critical gaps in CBRN preparedness by leveraging existing medical knowledge and provides a scalable framework for future countermeasure development. Our approach demonstrates the value of computational text mining in accelerating the identification of viable treatment options for complex threat scenarios while minimizing resource expenditure.

WG 1 (Chemical, Biological, Radiological and Nuclear materials)

Novel Approaches for Developing New Oxime Reactivators of OPNA-Inhibited Cholinesterase

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There are three components in the antidotal medical mixture used toward organophosphorus nerve agents (OPNA) poisoning: 1. oxime reactivator of OPNA-inhibited acetylcholinesterase (AChE), (e.g. 2-PAM, HI-6), 2. Anticholinergic drug (e.g. atropine, scopolamine) and 3. anti-convulsant (e.g. diazepam, midazolam). Despite extensive translational research over the last 50 years only few antidotal drugs were introduced to clinical use and there are still efficacy gaps to surmount in the treatment of certain OPNA intoxications. In particular, insufficient recovery, long term neurotoxic effects and fatalities have been observed during treatment of respiratory and skin-exposure to the A-series Novichoks nerve agents. We believe that the key component of the antidotal mixture is the oxime reactivator that displaces the OPNA from the covalent OPNA-AChE complex. Based on HTS-driven approach, we have recently discovered new non-quaternary oximes that are efficient and safe reactivators of sarin- and VX-inhibited BChE (Amitai et al. Comms. Biol. 2021). These non-quaternary oximes could potentially penetrate through the blood-brain barrier (BBB) and reactivate brain ChEs. In addition, during the last two years we have been focused on the development of new ketoximes rather than clinically approved aldoximes. The notion is that the spontaneous degradation of Phosphoryl-Ketoxime intermediate formed during reactivation of OPNA-AChE is catalytic, allowing turnover of the oxime for multiple reactivation cycles, effectively reducing the dose required for reactivation. In contrast, aldoximes reactivators produce a nitrile upon hydrolysis of their respective phosphoryl-oxime intermediate, an irreversible process. Therefore, we have prepared new ketoximes with enhanced nucleophilic potency. This project involves newly synthesized compounds that include substitution of aromatic rings by halogens (e.g. F and Cl) as an electron withdrawing group (EWG) as well as lipophilic group. The EWG effect is expected to lower the pKa of the ketoxime group and lipophilic efficiency is predicted to increase by Chlorine (Cl) substitution. Lower pKa values could induce higher concentration of oximate anion at physiological pH (7.4). The oximate anion is an active nucleophilic species that attacks the bound OP during reactivation. Indeed, calculated pKa and log P values (ACD Labs) demonstrate decrease in pKa values from 9-10 to pKa 7-8 together with increase in log P of Cl-substituted ketoximes compared to non-