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The Medicinal Chemistry of Bioterrorism

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A bioterrorism attack constitutes the deliberate release of biological warfare agents (BWAs) to cause illness or death in humans, animals or plants. BWAs can be used to target an individual, a group, or a population; they are typically found in nature and can be altered to increase their virulence, resistance, or ability to disperse. Deployment of BWAs can result in life-threatening disease, widespread fear and panic, economic loss, and breakdown of key infrastructure modalities via direct contamination of food and water supplies, saturation and overloading of healthcare systems, and disruption of energy and transportation networks; risks to warfighters continue to be especially high. BWAs can be difficult to detect, and infected hosts may not display definitive symptoms of illness for hours to days, at which point effective treatments are limited to nonexistent; early detection and treatment are therefore crucial. Pathogens of concern can either be contagious – communicable threats that spread rapidly through a group, population and/or farm crops, possibly causing epidemics – or may harm individuals while not being generally transmissible from one host to another. Some BWAs, such as anthrax in spore form, can survive dormant in the environment for weeks to years and may cause damage long after the initial attack has taken place. Available countermeasures to BWAs vary significantly depending on type of agent, route of exposure, and mechanism of action: some bacterial agents can be treated by antibiotics and/or vaccines, while treatment of viral agents and biological toxins is limited to preexposure vaccines (where those are available) and antitoxins.

A comprehensive plan to counter bioterrorism in the 21st century must prioritize investment in the basic and applied scientific research required for new anti-biowarfare drug development, as well as research toward new pathways to enhance immunity to bioterror agents. Recent work in these areas has been strongly focused on new preexposure vaccines and immunopotentiators, together with postexposure therapeutics to be administered in the immediate aftermath of an anthrax attack – for example, small molecules targeting the anthrax toxin lethal factor (LF) enzyme, a zinc hydrolase chiefly responsible for anthrax-related cytotoxicity. A drug capable of counteracting the lethal factor is expected to significantly diminish the threat of anthrax as a bioweapon, and is also expected to find application in veterinary medicine and in developing nations where textile workers and farmers are still vulnerable to non-terrorism-related anthrax infections. However, the LF enzyme is a challenging drug target; although progress has been made toward the design of new small-molecule antitoxins, none has yet reached the market. More research is urgently needed, as the average development time of a new drug or vaccine is ten or more years, and the mechanism by which the toxin acts is not fully understood.

Recently, novel drug design strategies incorporating computer simulations, high-throughput screening (HTS) of molecular libraries, and structural biology approaches have been designed and implemented, leading to several promising new drug scaffolds that are currently under investigation. Pharmacophore mapping, a technique in which computer models of known drug-target interactions are used to search molecule databases for new candidates, has proven useful for pinpointing potential anti-anthrax drugs, as has three-dimensional quantitative structure-activity relationship (3D-QSAR) modeling. “Lead-hopping” techniques such as topomeric searching, where a highly active but pharmacokinetically compromised compound is used as a template to “hop” to new structures that exhibit similar three-dimensional shapes but different functional groups – in order to retain biological activity while avoiding impediments to effective *in vivo* metabolism – have shown particular promise for identifying small molecules that can be “built” or optimized into new drugs. Advances in high-throughput screening (HTS) technologies, where large compound libraries can be rapidly screened *in vitro* for activity against the lethal factor, have also facilitated new compound identification, but biological assays are costly, and compound follow-up and optimization normally follow a cyclical process that takes months or even years before a promising candidate can proceed to cell-based assays and subsequent *in vivo* analysis. Given the time-consuming and complex nature of anti-BWA drug discovery and mechanistic research, greater strategic and financial commitments in this area will be critical to staying ahead of the ever-increasing diversity and improved resilience/resistance of bioterror agents.

This special mini-issue of *Current Topics in Medicinal Chemistry (CTMC)* focuses on two key, complementary approaches to combating the threat of BWAs: immunopotential to enhance resistance to Select Agent bacterial pathogens, and the development and validation of computational modeling techniques to facilitate discovery and optimization of small-molecule anti-bioterror therapeutics including those targeting metalloenzymes such as the lethal factor. The contributions to this issue include original research as well as review material, covering a broad range of medicinal chemistry related topics and techniques including virtual screening, strategies for augmenting innate immunity, lead optimization, structural biology, statistical analyses, and docking and scoring.

Grateful acknowledgment is made to the authors of these manuscripts, as well as to the invited referees for their thorough and thoughtful reviews. The articles featured here offer novel insights into opportunities and challenges extant in the medicinal chemistry (and biochemistry) of bioterrorism, as well as specific methodologies, guidance, and recommendations for moving forward. It is our hope that this work will contribute to the ongoing national defense against biological terrorism-related events, and advance our Nation’s overall capacity to improve and protect health.

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