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## A Toxidromic Approach for Chemical Medical Countermeasure Development

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# Zwitterionic Functional Polymers Promote the Efficacy and Safety of Organophosphate Hydrolase (OPH) Against Chemical Warfare Agents

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Organophosphorus (OP) poisoning remains a major medical issue for public health, and nerve agents intimidate both soldiers and civilians in war zones. Numerous efforts have been devoted to searching for an effective prophylactic nerve agent bioscavenger to prevent the deleterious effects of these compounds. In particular, organophosphorus hydrolase (OPH) is a bio-scavenger protein highly effective in hydrolyzing OP compounds into biologically inactive products. Unfortunately, in vivo applications of OPH have been hindered by its inadequate circulation time and strong immunogenicity. The conjugation of a super-hydrophilic zwitterionic polycarboxybetaine (PCB) to OPH has been demonstrated to improve the pharmacokinetics (PK) and reduce the immunogenicity of OPH. However, due to the very low number of functional amine groups on OPH surfaces, it is hard to achieve very high-density PCB polymers around OPH in order to fully shield OPH from immune recognition and to completely eliminate the undesirable immune responses associated with OPH. Here we will demonstrate multiple chemical, physical and biological approaches based on different zwitterionic inert and proactive materials to shield or suppress the immunological response of proteins. Conjugation of these polymers completely eradicates protein immunogenicity, and prolong protein circulation time. These polymers will not only promote the translation of OPH from bench to clinic, but also revolutionize the field of protein conjugates. In this talk, zwitterionic immunosuppressive polymers will be highlighted. It is found that apoptotic cells can direct immune cells such as macrophages and dendritic cells to immunosuppressive phenotypes via externalized phosphatidylserine (PS) on their surface and thus induce immune tolerance even in inflammatory activated regions. Inspired by this natural phenomenon, a zwitterionic PS-mimic (ZPS) monomer and its polymers were developed. In contrast to the inert PCB polymers, which alleviate the immunogenicity of proteins by passively hiding their immunogenic epitopes from immune surveillance, ZPS polymers have been shown to actively suppress the immune system, resulting in immune tolerance towards their associated proteins. Such an immunomodulatory property of ZPS is particularly meaningful to OPH as its function in preventing immune responses does not require a high surface-coating density, which is favorable to fully address the immunogenic issues encountered by OPH and other proteins with low functional groups available. On the other hand, ZPS has been shown to retain the typical super-hydrophilic property of zwitterionic materials and the conjugation of ZPS could also significantly extend the circulation of protein in vivo, much like PCB.