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Metal–Phenolic Network Hydrogel Vaccine Platform for Enhanced Humoral Immunity against Lethal Rabies Virus

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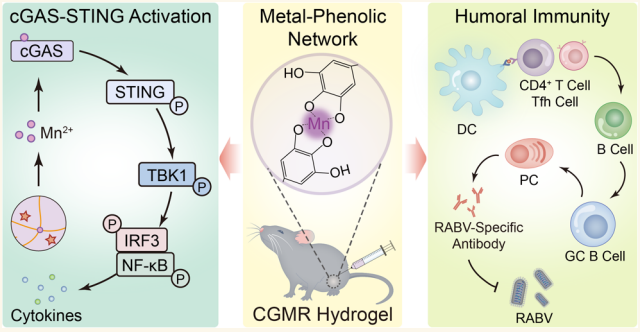
ABSTRACT: **Rabies, caused by rabies virus (RABV), is a zoonotic disease with a high mortality rate that has attracted global attention with the goal of eradication by 2030. However, rabies can only be prevented by appropriate and multiple vaccinations, which impede widespread vaccination in developing countries due to its high expenditure. Designing single-dose vaccines is a pressing challenge in the prevention of rabies and other infectious diseases. Herein, a metal–phenolic network (MPN)-based hydrogel vaccine (designated as CGMR) was developed to stimulate potent humoral immunity against RABV infection by a single immunization, resulting in 4.3-fold and 1.8-fold enhancements of virus-neutralizing antibody compared with that induced by inactivated RABV and alum adjuvant. The CGMR, cross-linked by phenol-modified chitosan with manganese ion, could prolong residence time by confining the antigen to the network of hydrogel, acting as a "hydrogel antigen depot". It also stimulated the activation of the cyclic guanosine monophosphate–adenosine monophosphate synthase (cGAS)-stimulator of interferon gene (STING) pathway, facilitating dendritic cell maturation and antigen presentation. The vaccine formulation recruited immunocytes and activated the germinal center, enhancing and sustaining humoral immune responses against the virulent RABV challenge. Collectively, this injectable manganese-based hydrogel vaccine provides a universal and ideal avenue for rabies and other infectious diseases.**



KEYWORDS: *rabies virus, injectable hydrogel vaccine, metal–phenolic networks, cGAS-STING adjuvant, humoral immunity*

Rabies is a highly fatal neurological disease caused by the rabies virus (RABV).[1] Once the virus reaches and replicates in the brain, patients enter the acute neurological phase and present two classical clinical presentations, furious or paralytic, both ultimately leading to coma and death.[2,3] Globally, more than 60,000 deaths occur annually owing to viral infection, predominantly in developing countries of Asia and Africa. Nearly 99% of these cases are caused by dog-transmitted rabies.[4,5] Vaccination remains the most efficient medical intervention for humans or animals owing to a lack of adequate and prompt treatments. However, achieving effective viral neutralization, whether for post- and pre-exposure, often requires repeated vaccination and/or the use of adjuvants, which significantly increases the immune cost and reduces vaccine coverage.[6] According to the global target for eliminating dog-mediated rabies by 2030, endorsed by numerous international organizations,[7] improving vaccine efficacy and expanding vaccine coverage are considered effective approaches.

Adjuvants play prominent roles in potentiating the immune responses of vaccines, especially for inactivated and subunit-based vaccines.[8] Nonetheless, only several adjuvants have been licensed for human and animal uses and have been confirmed to promote the strength, breadth, and persistence of immune responses. Among all adjuvants, aluminum salts remain the most widely used since 1926.[9] It prolongs the release of antigens via the "antigen depot" to enhance the immune response, which is considered to be the prevailing mechanism of action.[10,11] However, some studies have proved that aluminum can cause local swelling, inflammation, neuro-

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