**Traditional Medicine Combination Therapy Is A Promising Strategy for MRSA Infection**

Figure 1

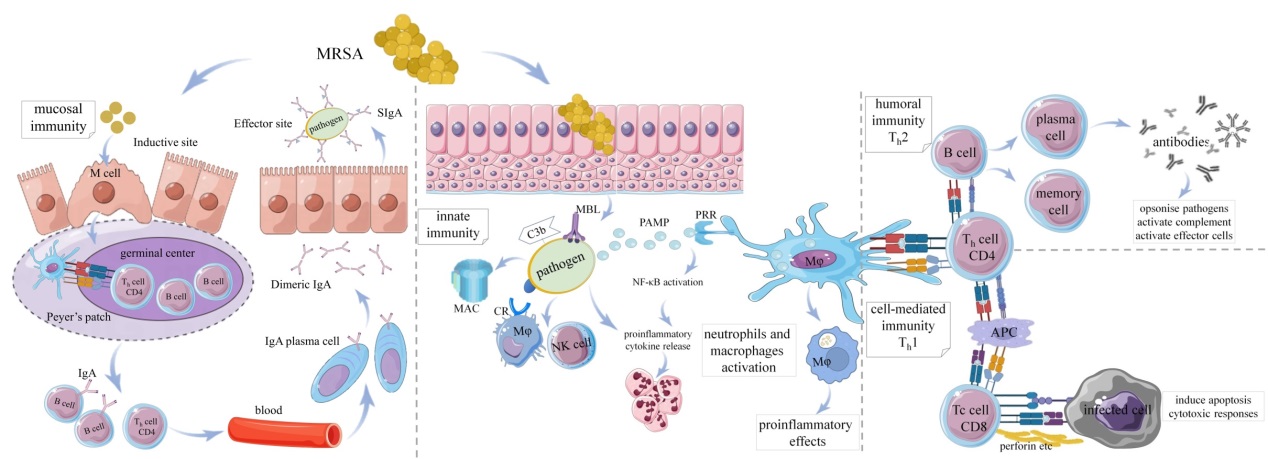
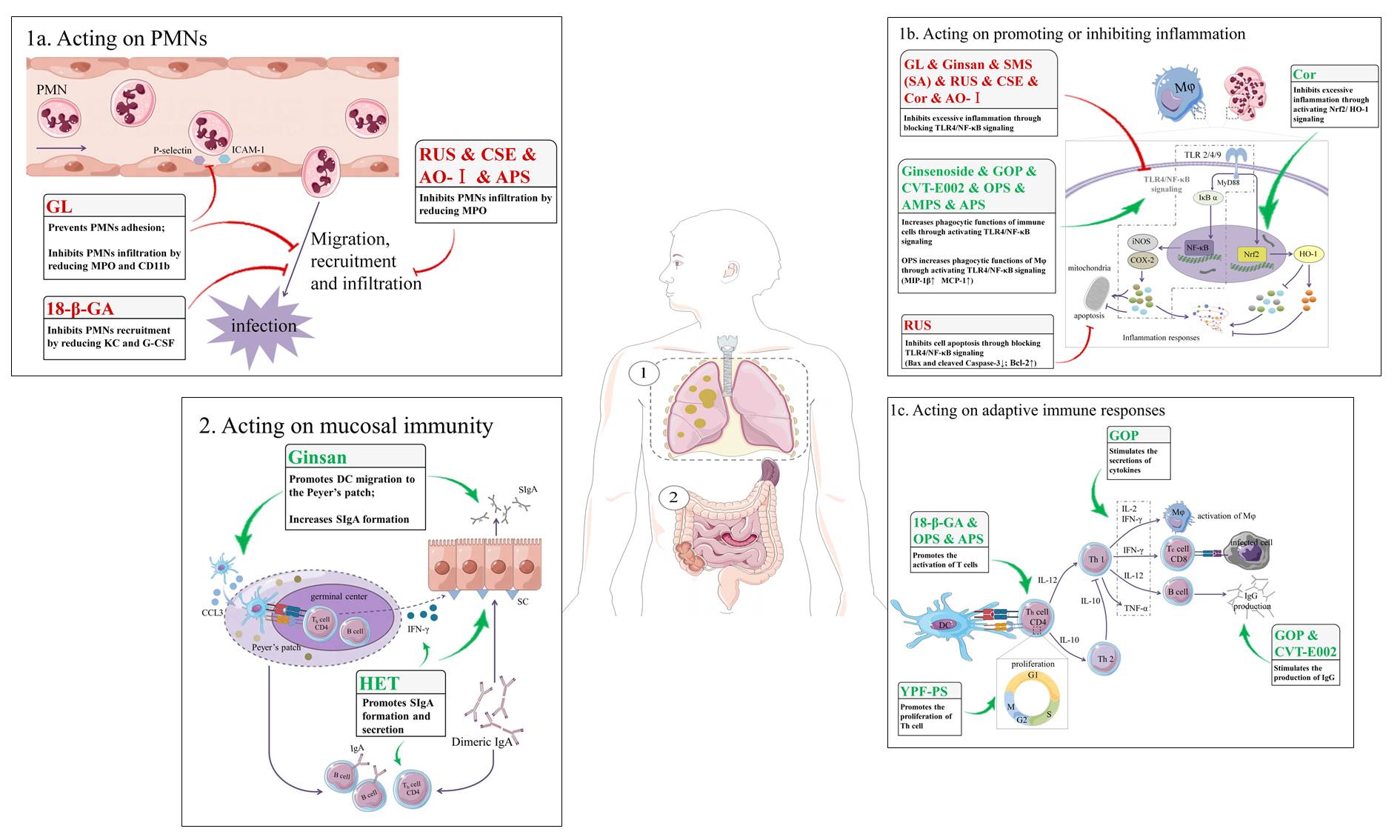


Figure 1. Overview of immune response mechanisms during MRSA infection. The body has three lines of defense against MRSA infections. (A) Mucosal immune response. The mucosal surface is in direct contact with pathogens. The key strategy of the mucosal immune response is to generate antigen-specific IgA antibodies in the external secretions. This process occurs at Peyer’s patches (PP), and its key function is the sampling of antigens. To facilitate this sampling, microfold (M) cells, specialized phagocytic cells in the PP, can directly swallow and transport antigens in the nasal or intestinal cavity to DCs via phagocytosis. In the PP, through antigen presentation, IgA-committed B-cell (IgA+ B cells) are induced to develop and finally produce dimeric (or polymeric) forms of IgA after proliferation and differentiation at effector sites. Ultimately, these forms of IgA become secretory IgA by binding to polymeric Ig receptors (SCs). SIgAs are then released into the nasal passage and intestinal tract, binding and “coating” offending pathogens, thus blocking pathogen invasion. (B) Innate immune response. The complement system is activated through the classical pathway, lectin pathway and alternative pathway. Some complement fragments, such as C3b formed by C3 convertases cleaving the C3 protein, can exert phagocytosis through binding with the complement receptor (CR). The membrane attack complex (MAC) is formed and directly leads to cell lysis. Moreover, other complement fragments, such as C3a and C5a, can trigger a series of chemotactic and proinflammatory responses to facilitate neutrophil migration to the site of infection. Neutrophils recruit and migrate to infection sites along a concentration gradient of chemokines secreted or released by activated host cells or complement components such as C5a. Finally, neutrophils are primed, activated and stimulate bacterial clearance by phagocytosis and bactericide. Gradually, the invading bacteria are killed, and any remaining neutrophils die off via apoptosis and are cleared by macrophages. (C) Adaptive immune response. As pathogens are degraded, antigenic peptides can be presented by dedicated antigen-presenting cells, such as DCs and Mφs, to T-lymphocytes, further activating the host adaptive immune response. When stimulated directly or indirectly, B cells differentiate and produce antibodies, which specifically bind with bacteria to eliminate pathogens. When bacteria enter the cells, antigen-specific T cells are stimulated and differentiate into CD8+ T cells. These cells recognize and specifically bind to infected cells (targeted cells) invaded by antigens, activate lysosomal enzymes in targeted cells, and finally lead to the lysis and death of targeted cells. The antigens in the cells lose are bound and immobilized by the antibodies and are then phagocytosed. Ultimately, MRSA infection is inhibited.

Figure 2.

(A) Targets of immune responses in the host’s immune defenses.



(B) Targets of immune responses in MRSA immune evasion strategies.

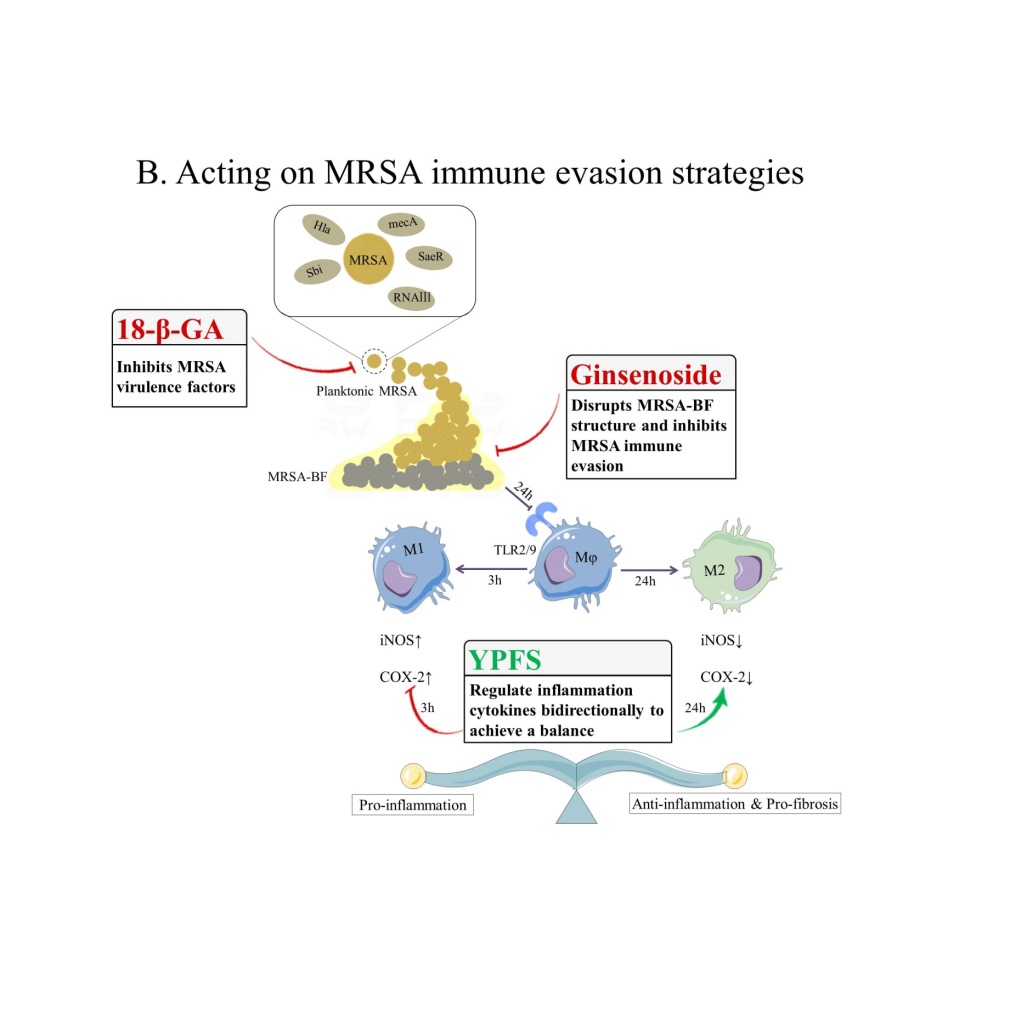


Figure 2. Main mechanisms of TCM therapies against MRSA infections. (A) Targets of immune responses in the lung and mucosa. 1a. Acting on PMNs; 1b. Acting on promoting or inhibiting inflammation; 1c. Acting on adaptive immune responses. 2. Acting on mucosal immunity. (B) Targets of immune responses in MRSA immune evasion strategies. PMN, polymorphonuclear leukocyte. ICAM-1, Intercellular adhesion molecule 1. GL, glycyrrhizin. 18-*β*-GA, 18-*β*-glycyrrhetinic acid. RUS, Ruscogenin. CSE, *C. sinensis* extract. AO-I, *Atractylenolide* I. APS, *Astragalus* polysaccharides. SMS (SA), Shengmai San (*Schisantherin A*). Cor, cordycepin. GOP, Ginseng oligopeptides. CVT-E002, a patented aqueous extract from *Panax quinquefolium* (*P. quinquefolius*). OPS, Ophiopogon polysaccharide. AMPS, *A. macrocephala* polysaccharides. Mφ, macrophage. HET, Hochuekkito. YPF-PS, polysaccharides derived from Yupingfeng San. Green arrows represent promotion. Red arrows represent inhibition.

Figure 3

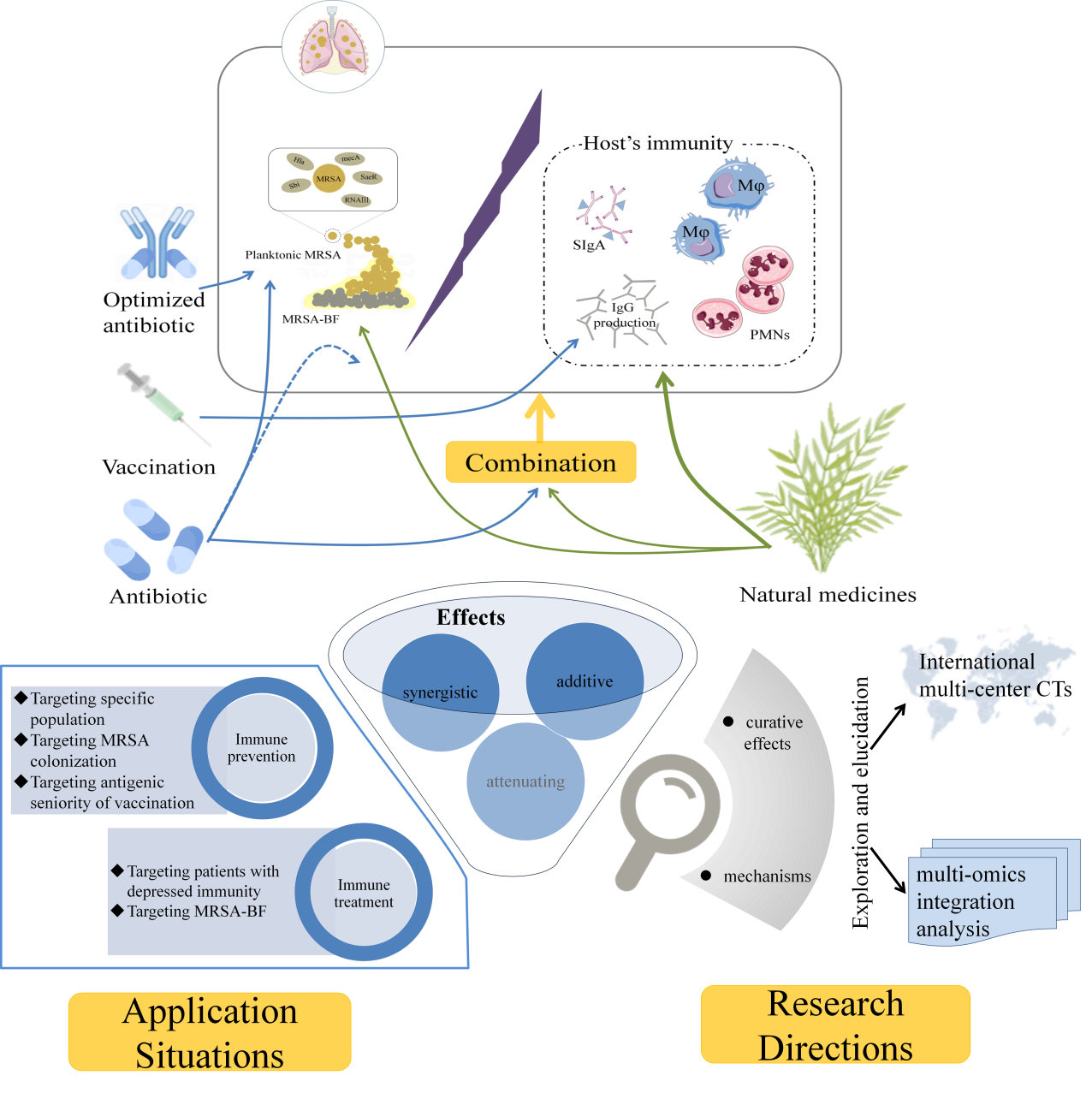


Figure 3. Overview of the combined efficacy of conventional therapies and TM therapies against MRSA infection. Combination with conventional therapies and TM therapies combats MRSA infection not only by inhibiting planktonic MRSA and MRSA-BF but also by regulating host immunity. The combination therapy may exert three effects: additive, synergistic and attenuating. Combination therapy can be used for both MRSA infection prevention and treatment. Furthermore, international multi-center CTs should be performed to confirm curative effects and multi-omics integration analysis should be used to elucidate the corresponding mechanisms.