SHIP-1 INHIBITORS FOR PROPHYLACTIC TREATMENT AND/OR PREVENTION OF INFECTIOUS DISEASES.

Summary:

Trained immunity can be defined as a de-facto innate immune memory that induces enhanced inflammatory and antimicrobial properties in innate immune cells. Innate immune cells can be trained to exhibit an enhanced and lasting response to subsequent infections with microbial components. Importantly, this boosted response can be triggered against pathogens diverse from those that induce the training. However, improving the heterologous response of trained innate immune cells remains complicated. CNIC, Syracuse University and SUNY Upstate Medical University researchers have discovered that the use of SHIP-1 inhibitors, enhance the non-specific response of trained innate immune cells. This increased activity may offer an improved prophylactic treatment or prevention of subsequent infections.

Innovative aspects:

The general view that only adaptive immunity can build immunological memory has been challenged. In organisms lacking adaptive immunity, as well as in mammals, the innate immune system can mount a recall resistance to reinfection; a phenomenon termed "trained immunity" or "innate immune memory". Trained immunity can be defined as a de-facto innate immune memory that induces enhanced inflammatory and antimicrobial properties in innate immune cells, responsible for an increased heterologous response to subsequent infections and improved survival of the host. The discovery of trained immunity may open the door for novel vaccine approaches, new therapeutic strategies for the treatment of immune deficiency states, and modulation of exaggerated inflammation in autoinflammatory diseases.

Innate immune cells challenged with certain stimuli undergo long-lasting changes that result in improved response to a second challenge by the same or even different (heterologous) microbial insults. Innate immune cells can be trained to exhibit an enhanced and lasting response to subsequent infections with microbial components. However, there is a technical problem, which is how to further improve the non-specific response of trained innate immune cells. CNIC, Syracuse University and SUNY Upstate Medical University researchers solved this problem by demonstrating that trained immunity in myeloid cells can be further enhanced by means of the use of compounds acting as enhancers, which are directed to the inhibition of a specific target.

Researchers demonstrated that the use of a bacterial component as a stimulus, trained macrophages from mice with a specific SHIP-1 deletion in the myeloid compartment. Moreover, researchers

demonstrated that *in vivo* SHIP-1 deficiency in the myeloid compartment improves protection conferred by trained immunity. Notably, pharmacological SHIP-1 inhibition in both mice and human peripheral blood mononuclear cells (PBMCs) enhanced pro-inflammatory cytokine production and a better protection, providing a potential therapeutic approach to boost trained immunity.

CNIC, Syracuse University and SUNY Upstate Medical University researchers used low dose of bacterial component as an example of stimulus, conferring a first stimulus responsible for reprogramming the immune response. Animal models having SHIP-1 inhibited and trained with this stimulus, showed a remarkable increased survival rate. Thereof, the response of trained innate immune cells to subsequent infections can be boosted by the inhibition of SHIP-1.

Competitive advantages:

- *In vivo* SHIP-1 deficiency in the myeloid compartment improves protection conferred by trained immunity.
- The pharmacological SHIP-1 inhibition provides a potential therapeutic approach to boost trained immunity.
- The administration of one specific SHIP-1 inhibitor was effective in boosting bacterial-induced resistance to *Candida* infection.
- SHIP-1 is defined as a new target to improve bacterial-induced myeloid-dependent trained immunity.

Key words: trained immunity, innate immune cells, SHIP-1 inhibitors, heterologous response, infectious diseases, myeloid cells.

Technology type: trained immunity, non-specific prophylactic treatment, prevention, infectious diseases.

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Stage of development: tested in animal models.

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