Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Federal Department of Home Affairs FDHA
Federal Food Safety and Veterinary Office FSVO
Research Management

Harnessing trained immunity to enhance resistance of piglets against infections

Razieh Ardali[1,2], Obdulio Garcia Nicolas[1,2], Catherine Ollagnier[3], Artur Summerfield[1,2]
[1]Institut für Virologie und Immunologie (IVI), 3147 Mittelhäusern
[2]Department of Infectious Diseases and Pathobiology, Vetsuisse Faculty, University of Bern, 3001 Bern
[3]Pig Research Unit, Agroscope, 1725 Posieux, Switzerland

Key words
Immunomodulation, trained innate immunity, pigs, infectious diseases.

Aim of the study

There is an urgent need for alternatives to antibiotics to ensure animal health and consumer safety. This project applied new immunological concepts based on innate immune memory to limit animal health damage caused by pathogens. To this end we identified immunomodulatory compounds *in vitro* with potential ability to enhance non-specific resistance of piglets against infection, or alternatively enhance the animal's resilience, if infected. We anticipate that such compounds will improve pig health and welfare and contribute to improved sustainability and safety in pig production.

Material and methods
Using a porcine monocytic cell culture model for innate immune memory, a large panel of ligands targeting pathogen recognition receptors were screened for their ability to train monocyte-derived macrophages for enhanced cytokine responses. A strong focus was placed on beta-glucans and bacterial cell wall compounds but also a ligand with known immunomodulatory activity were included. In a second step, selected ligands were tested for their ability to train the piglet's immunity for a potential increased resistance against infection. To this end, pigs were treated with the compounds 14 days before weaning and then vaccinated with a bacterin vaccine containing lipopolysaccharide as adjuvant. As readout we employed clinical evaluation, cytokine ELISAs, antibody responses, and a transcriptomic profiling of blood leukocytes.

Results and significance
Immunostimulatory profiles from a large panel of compounds were obtained. In general, most compounds induced a tolerogenic status in the macrophages *in vitro*. The only compound that promoted the secondary response of macrophages was muramyl dipeptide. *In vivo*, we tested a beta-glucan being one of the most established inducer of trained immunity in murine models, and found this compound to dampen the inflammatory response induced by the vaccine, without affecting vaccine-induced antibody levels. We also identified and tested a non-microbial immunomodulators which efficiently dampened inflammation. In conclusions, our data indicate that beta-glucans are unable to train the innate immune system of piglets. Nevertheless, the identification of pathways reducing inflammatory responses are also of high interest and clinically applicable to enhance resilience to infection or reduce side-effects of vaccines. Follow-up *in vivo* investigations are required to identify the potential of muramyl dipeptide to train innate immunity, and to evaluate the clinical and economical potential of the identified immunomodulatory interventions.

Publications, posters and presentations
Harnessing Trained Immunity to Enhance Resistance of Piglets against Infections. Ardali et al., 5th International Symposium on Trained Immunity. Naples, Italy May 29-31, 2023.

In-vitro screening of immunostimulatory ligands for induction of trained immunity in porcine monocyte/macrophages. Ardali et al., 13th International Veterinary Immunology Symposium. Kruger National Park, South Africa, Nov 17-22, 2023.

Harnessing Trained Immunity to Enhance Resistance of Piglets against Infections. Ardali et al., 13th International Veterinary Immunology Symposium. Kruger National Park, South Africa, Nov 17-22, 2023.

***Project** 1.20.01*

***Project duration:** September 2020 - August 2023*