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Towards enhancing the longevity of vaccine-induced immunity against foot-and-mouth disease virus

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Key words
Vaccine adjuvant, neutralizing antibody response, system vaccinology, foot-and-mouth disease virus

Aim of the study
Foot-and-mouth disease virus (FMDV) remains amongst the most important pathogen threatening the world agricultural economy. In endemic regions, control of FMD is dependent on vaccination programs but currently available FMD vaccines only provide a short duration of immunity. To re-enforce the power of vaccination campaigns our aim is therefore to translate current immunological knowledge obtained from basic immunology into large animals such as cattle, sheep and pigs towards improving the duration of immunity against FMDV in these animals.

Material and methods
To construct a vaccine with enhanced immunogenicity a large panel of Toll-like receptor ligands (TLRL) was screened and characterized in cell cultures with different antigen presenting cells towards selection of optimal ligands efficient in target species of FMDV. Selected TLRL were formulated together with the antigen (inactivated FMDV 146S antigen) in a liposomal nanoparticle based delivery system. The vaccines were tested in sheep using a system vaccinology readout as well as their ability to induce neutralizing antibody responses.

Results and significance

Our studies demonstrate that the combination of particular TLRL enhances antibody response in terms of increasing the number of days the neutralizing antibody titer was above a critical value associated with protective immunity. Although the experimental vaccine had less side effects, it was inferior to mineral-oil adjuvanted vaccine in terms of inducing high level and long-lasting antibody responses. Nevertheless, the project represents a milestone in veterinary vaccinology as we were able to develop a system immunology-based approach to identify early predictors of vaccine-induced antibody responses by analyzing the gene expression profile in peripheral blood collected three and seven days post vaccination. These predictors represent groups of highly interacting genes termed “blood transcriptional modules” (BTM) and some correlated to antibody responses. Correlating BTM expressed three days after vaccination were related to the innate inflammatory and antigen presentation. On day seven, many correlating BTM were now related to B cells and cell cycle, reflecting early events in the adaptive B-cell response. Thus, the present system immunology approach enables to identify in the peripheral blood early vaccine-induced response correlating to high antibody responses found several weeks later. It should be applicable to other species and will be very useful to both, the identification of efficient vaccine adjuvants and to find factors relating to low vaccine responders. Taken together, although the aim of developing a vaccine able to induce a long duration of immunity was not achieved, the results and the methodology developed will be very precious for future vaccine projects aiming to improve the immunogenicity of inactivated vaccines. Compared to attenuated viral vaccines and viral vector

vaccines, inactivated vaccines do not raise safety and environmental concerns, and can be developed and brought to the market in a shorter time, as compared to live virus vaccines in case of emerging pathogens. Also, for safety reasons countries free of disease neighboring endemic areas will often prefer inactivated vaccines to protect their animals. Such inactivated vaccines can often be made DIVA (differentiating infected from vaccinated animals)-compatible by the use of serological tests targeting non-structural proteins expressed only during virus replication. Therefore, continued research on vaccine adjuvants based on the results obtained in this project is important and promising.

Publications, posters and presentations

Braun, R. O.; Brunner, L.; Auray, G.; Baumann, A.; Obdulio, G.-N.; Python, S.; Zumkehr, B.; Collin, N.; Gaschen, V.; Stoffel, M.; Barnier-Quer, C.; Summerfield, A. Development of a TLR-ligand adjuvanted liposome-based vaccine to enhance the duration of immunity GCB Symposium, 04.02.2016, Bern, Switzerland (poster)

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Braun, R. O.; Python, S.; Auray, G.; Summerfield, A. Response of porcine peripheral B cells to stimulation with Toll-like receptor ligands. International Veterinary Immunology Symposium, 16.08.2016 - 19.08.2016, Gold Coast, Australia (oral presentation).

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Braun R. O.; Application of systems vaccinology to the veterinary field using a Toll-like receptor ligand adjuvanted liposomal vaccine targeting antigen presenting cells. PhD Thesis, Graduate School for Cellular and Biomedical Sciences, University of Bern.

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