6-12-2022

RHABDO-LIKE RECOMBINANTE (VLPs), a novel veterinary rabies vaccine: Safety and efficacy trials in pets and cattle

Claudio Prieto

Diego Fontana

Federico Marsili

Ricardo Kratje

Marina Etcheverrigaray

RHABDO-LIKE RECOMBINANTE (VLPs), A NOVEL VETERINARY RABIES VACCINE: SAFETY AND EFFICACY TRIALS IN PETS AND CATTLE

Claudio Prieto, School of Biochemistry and Biological Sciences, Universidad Nacional del Litoral., Argentina. dfontana@fbcb.unl.edu.ar
Diego Fontana, School of Biochemistry and Biological Sciences, Universidad Nacional del Litoral. Argentina.
Federico Marsili, Claudio Prieto, School of Biochemistry and Biological Sciences, Universidad Nacional del Litoral. Argentina.
Ricardo Kratje, School of Biochemistry and Biological Sciences, Universidad Nacional del Litoral., Argentina.
Marina Etcheverrigaray, School of Biochemistry and Biological Sciences, Universidad Nacional del Litoral, Argentina.

Key Words: Rabies, Virus-like particles, vaccines, neutralizing antibodies, recombinant

Rabies is a viral fatal disease transmitted to humans from bites of infected animals. Due to nearly 95 % of human infections are related with dog bites, the WHO, OIE and FAO agreed in the implementation of a worldwide plan for the elimination of dog-mediated human rabies death by 2030. On the other hand, in some Latin-American countries paralytic bovine rabies transmitted by vampire bats causes economic losses to the farming industry. In this context, it is important to develop an economic vaccine that could be produced in a short period of time.

Our research group have been working in the development and validation of a recombinant rabies vaccine based on virus-like particles (RV-VLPs), expressing the rabies glycoprotein in HEK293 cells[1]. Performing a rational design, we carried out the expression vectors construction, stable cell line development and the full biochemical and morphological characterization of the expressed RV-VLPs. On the other hand, the immune response triggered by these VLPs in mice was analysed, demonstrating that this new antigen is able to induce a potent humoral immune response with high titers of neutralizing antibodies. Furthermore, protection against rabies virus challenge was confirmed in NIH potency test assays, demonstrating that RV-VLPs are an excellent new generation and virus-free vaccine candidate.

Later, we obtained a stably producer clone able to continuously express RV-VLPs to the culture supernatant and grow in suspension conditions with serum free medium (SFM)[2]. The production of the VLPs in 1 and 5 L bioreactors operated in perfusion conditions was performed, demonstrating that this rabies vaccine candidate can be produced with high productivity in a conventional recombinant protein production facility, without virus contention o high biosafety levels needed.

Furthermore, with the goal of obtaining a cost-effective bioprocess able to be transferred to the veterinary market, we worked in the process optimization in order to reduce the SFM cost; due to this is one of the principal expenses. Thus, we achieve to adapt our producer clone to a non-expensive in-house culture medium to be used for perfusion, reducing up to 50 % of the global cost of the culture process[3].
In this work, we optimized the vaccine formulation, studying the use of different adjuvants with the aim of improving the vaccine potency with a minimum antigen concentration required. We obtained a final RV-VLPs formulation, using a new adjuvant based on cage-like particles with low surface charge density containing Quil-A® as an immune response stimulator. Rabies VLPs with this formulation are stable for more than 2 years at 4 °C, obtaining a potency higher than 1 IU/ml when NIH assay was performed after that period of study. Besides, we carried out safety and serology trials in dogs, cats and livestock, demonstrating that the RV-VLPs are able to induce a long-lasting immune response in target species, comparable with the commercial vaccines based on inactivated rabies virus. Besides, following CFR and VICH guidelines we could demonstrate that RV-VLPs are safe to be used as a rabies vaccine in the studied species.

All these results showed that the obtained RV-VLPs, together with the entire bioprocess developed, are an excellent vaccine candidate that currently is being transferred to the animal health market.

1. Fontana et al. Vaccine 32 (2014) 2799–2804.
2. Fontana et al. Vaccine 33 (2015) 4238-4246.
3. Fontana et al. BMC Proceedings (2018) 12(Suppl 1):P-204