VAC_03 - An alphavirus-derived replicon polyvalent RNA vaccine induces neutralizing antibodies in mice against omicron SARS-CoV-2 variant of concern

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Introduction: Vaccination is the most effective approach to control the COVID-19. However, the literature has shown that neutralization of omicron is impaired by prophylaxis with wild type spike RNA vaccines.

Objectives: Our aim was to evaluate the efficacy of a polyvalent alphavirus-derived replicon (Rep) RNA vaccine to induce neutralizing antibodies (nAB) against omicron (B.1.159) pseudoviruses after D614G Rep-RNA pre-vaccination in mice. RepRNA encoding D614G and the spikes from VoCs alpha, beta, gamma, and omicron were produced by *in vitro* transcription and formulated with a cationic nanocarrier (LION™).

Methodology: Balb/c mice were previously immunized with two doses of 1μg LION/RepRNA-D614G 28 days apart, followed by vaccination with two doses of 1μg LION/RepRNA-omicron or polyvalent (0,2μg of each RepRNA-VoCs). The nAB was determined by pseudovirus neutralization assay, using phenotypic high content analysis with the percentage of ZsGreen positive cells as the readout. The plasma neutralization potency (pNT_{50}) was calculated by non-linear regression from a plasma dilution curve from 1:40 to 1:2560.

Results: Pre-vaccinated mice were able to neutralize D614G pseudoviruses regardless of the vaccination with LION/RepRNA-omicron or polyvalent. Pre-vaccinated animals which received LION/RepRNA polyvalent presented the highest pNT_{50} (3324), significantly more potent than mice that received LION/RepRNA-omicron pNT_{50} (1210). Animals only vaccinated with LION/RepRNA-polyvalent neutralized better D614G pseudoviruses than mice immunized only with LION/RepRNA-omicron. The pre-vaccination with LION/RepRNA-D614G impaired the neutralizing capability of omicron pseudoviruses in animals vaccinated with LION/RepRNA-omicron.This phenotype was reverted using LION/RepRNA polyvalent (pNT_{50} equal to 36 and 277, respectively). Two doses only of either LION/RepRNA-omicron or polyvalent induced more neutralizing antibodies than in pre- vaccinated mice which received LION/RepRNA-omicron (pNT_{50} equal to 442 and 415, respectively).

Conclusion: Our results confirmed the previously reported data and showed the use of a LION/RepRNA-polyvalent vaccine can revert the phenotype. A polyvalent LION/RepRNA including the main VoCs can overcome the problem of neutralization escape.

Keywords: Covid-19, polyvalent vaccine, RNA