

## Nanogel Engineering for Nasal Immunization: Evaluation of delivery strategy

Ana Sonzogni<sup>1,2</sup>; Victor Pilicita<sup>1</sup>; Jakes Udabe<sup>3</sup>; Paula Cacik<sup>4</sup>; Ivan Marcipar<sup>4</sup>; Verónica Gonzalez<sup>1,4</sup>; Roque Minari<sup>1,2</sup>; Marcelo Calderon<sup>3</sup>

<sup>1</sup> Group of Polymers and Polymerization Reactors, INTEC (Universidad Nacional del Litoral-CONICET) Santa Fe, Argentina.

<sup>2</sup> Facultad de Ingeniería Química, Universidad Nacional del Litoral, Santa Fe, Argentina.

<sup>3</sup> POLYMAT, Applied Chemistry Department, Faculty of Chemistry, University of the Basque Country UPV/EHU, San Sebastián, Spain

<sup>4</sup> Facultad de Bioquímica y Ciencias Biológicas, Universidad Nacional del Litoral, Santa Fe, Argentina.

asonzogni@santafe-conicet.gov.ar

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Although the conventional and current vaccination route is injection, most pathogens enter to the host through the mucosal pathway. Consequently, available vaccines cannot prevent infection, but rather protect against the development of the disease. In contrast, vaccination in the site of pathogen entry, has the potential to directly prevent infection.<sup>1</sup> However, this route remains underexploited because of physiological barriers such as enzymatic degradation and rapid mucociliary clearance, which limit antigen stability and residence time. Nanoparticles, particularly nanogels (NGs), have emerged as promising carriers to overcome these limitations by protecting antigens and enhancing cellular uptake.<sup>2</sup> In this study, we synthesized poly(*N*-vinylcaprolactam) (PVCL) NGs with different properties and functionalities facing nasal administration of antigens. NGs were synthesized employing two crosslinkers (*N,N*-methylenebisacrylamide, BIS and *N,N*-bisacrylylcystamine, BAC) at different concentrations and combinations. BAC-containing NGs degrade in the presence of glutathione (GSH), generating thiol groups that promote mucoadhesion, while BIS-based NGs exhibit a negative charge favoring mucopenetration. All NGs displayed thermoresponsive behavior and high antigen-loading efficiency (94–98%) using ovalbumin (OVA) as a model antigen. BAC-containing NGs showed GSH-dependent degradation and mucoadhesion both dependent on BAC content. In nanogels containing BAC, OVA release depended on the presence of GSH, with release kinetics dependent on BAC content. Intranasal immunization with OVA-loaded NGs induced strong systemic humoral responses in all cases. At the mucosal level, BIS-containing nanogels demonstrated a strong ability to induce antigen-specific IgA secretion, significantly overcoming the low mucosal immunogenicity of free OVA. Overall, PVCL NGs demonstrated strong potential as nasal vaccine platforms. Among them, BIS-based NGs showed superior performance, likely due to sustained antigen release prolonging antigen exposure to the nasal mucosa and their ability to act as immunostimulatory structures.

### REFERENCIAS

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