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Development of an anti-idiotypic Mab as cancer vaccine: From discovery to approval

kathya Rashida de la Luz Hernandez[1], Julio Santo-Tomás[1], Yoan Machado[1], Yadira Aguilar[1], Svieta Víctores[1], Yadira Prieto[1], Orlando Morales[1], Amparo Macías[1], María C Barroso[1], Tania Crombet[1], Eduardo Ojito[1], Yudisleydis Fortunato[1], Yanitzia Crespo[1], Dasha Fuentes[2], Danais Vidal[1], Yamilet Rabasa[1], Blanca Pacheco[1], Yulier Alvárez[1], Grisel Rodríguez[1], Adolfo Castillo[1] and **Ana M Vázquez[1]**

[1]Center of Molecular Immunology, Cuba

[2]National Center for Production of Laboratory Animals, Cuba

Background & Novelty: Racotumomab (1E10) is a murine anti-idiotypic antibody that mimics N-glycolyl-GM3 gangliosides. This antibody has been tested in some countries as an anti-idiotypic vaccine adjuvated in Al $(OH)_3$ in several clinical trials Phase II and III for NSCLC, melanoma and breast cancer. Recently this product was approved for treatment for NSLC by regulatory authorities in Cuba and Argentina. This study describethe novel and complete development strategy allowed taking the product from the original idea in the laboratory to test the concept in advanced clinical trials and approval, including its scale-up and comparability studies.

Experimental Approach: Initially the product was obtained from mice ascites fluid (AF), however a new pilot scale cGMP process based in stirred tank continuous mode cell culture using protein free medium was developed (ST). Further the production was scaled up to 1000 L bioreactor and a culture medium was optimized in order to increase productivity and cell growth. Bioequivalence between vaccine products obtained from ascites, different stirred tank scales and different cell culture media through a comparability tests was studied. Also, the influence of pH, ionic strength and phosphate concentration of buffer on the adsorption of the Mab to the aluminum gel was investigated. Formulations with different adsorption percentages and antibody/adjuvant ratios were characterized by DLS. Different characteristics as primary, secondary and tertiary structure, micro heterogeneity, identity, purity and biological activity of obtained Mabs, as well as vaccine formulation characteristics as stability, absorption to $AlOH_3$, immunogenicity and antitumor activity *"in vivo"* were analyzed. Techniques like mass spectrometry, liquid chromatography, circular dicroism, fluorescence, SDS-PAGE and immuno detection. In case of *in vivo* analysis, two animal models were used (Leghorn chickens for immunogenicity and mouse for anti-tumoral activity of vaccine).

Results & Discussion: Some differences were observed like charge heterogeneity and glycans attached to Fc-γ, mainly due to varying amount of sialylated species, asparagine deamination and oxidation in each condition. These characteristics did not affect the immune response elicited in chicken and antitumor effect on F3II carcinoma model. Moreover optimization of product formulation significantly increased the percentage of adsorbed protein to alumina and stability. *In vivo* experiments using Leghorn chickens were performed to evaluate effects on immunogenicity of the different vaccine formulations. However no influence of the adsorption and the racotumomab/Alumina ratio on the immunogenicity of the vaccine was observed. In summary, the introduction of a well-established process platform for the production of monoclonal antibodies, which led to increased levels of vaccine safety and reducing production costs, yielded a product very similar in each case, enabling the scaling and clinical development of the product until its health record.

katiar@cim.sld.cu