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La Tapa (Ver p. IV)
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LXII ANNUAL MEETING OF ARGENTINE SOCIETY OF CLINICAL INVESTIGATION (SAIC)

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LXV ANNUAL MEETING OF ARGENTINE SOCIETY OF IMMUNOLOGY (SAI)

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Palais Rouge– Buenos Aires

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LA TAPA

María Esther Gené, **Imagen ígnea**, 1996.

Acrílico sobre tela, 110 x 95 cm. Cortesía de la Comisión Nacional de Energía Atómica, Predio TANDAR, Centro Atómico Constituyentes. Presidente de la Comisión Organizadora de la Exposición Permanente: Dr. A.J.G.Maroto.

María Esther Gené nació en Buenos Aires. Cursó Historia del Arte y Estética con Blanca Pastor y Nelly Perazo. Se inició en el taller de Centa Bertier y continuó su formación con Miguel Dávila. Participó del grupo de investigación plástica que dirigió Emilio Renart. Integró el Grupo Gen y formó el Grupo Fusión. Realizó numerosas exposiciones colectivas e individuales (Museos Municipal de Bellas Artes de Luján, Fernán Félix de Amador, de Arte Moderno de la Ciudad de Buenos Aires, Fundaciones San Telmo y Banco Mayo, Fundación Andreani, Patio Bullrich, Galería Kristel K., Salón ICCED de Pintura, entre otros). Sus obras se encuentran en colecciones privadas de Argentina, México, Alemania, España, Uruguay y EE.UU.

[1] Comisión Nacional de Energía Atómica. Artistas Plásticos con la CIENCIA, Centro Atómico Constituyentes, Predio TANDAR, Buenos Aires, 1999; En: *http://www2.cnea.gov.ar/xxi/artistas/artistasplasticos.htm*

each) plus adjuvants, early release of TNF-α (6 hs, 340.5±191.3 pg/ml) and IL-1β (48 hs, 456.3±195.3 pg/ml) were detected. When HD PBMC were stimulated only with adjuvants, TNF-α and IL-1β release was higher (TNF-α: 1059±470 pg/ml; IL-1β: 1650±555 pg/ml). CSF-470 cells RNAseq analysis revealed an anti-inflammatory expression pattern, including TGF-β and IL-10 overexpression, that could partially mediate the hampered cytokines production, mainly promoted by BCG. On the other hand, IFN-γ release was also detected, but only in some HD PBMC with CSF-470 cells plus adjuvants cocultures (48 hs, 226,6±150 pg/ml), thus showing a high dependency on HD PBMC response to BCG. In conclusion, adjuvants, mainly BCG, were required to induce local inflammation in the presence of CSF-470 vaccine cells, given the anti-inflammatory pattern of cytokine expression, thus helping to create a favorable context for vaccine antigens to be processed and present.

Keywords: cutaneous melanoma; immunotherapeutic vaccine; adjuvants; cytokines

(518) ***IN VIVO* IMMUNOGENICITY ANALYSIS AND *IN VITRO* STABILITY CHARACTERIZATION OF NEW DE-IMMUNIZED RECOMBINANT HUMAN IFN-ALPHA (RHIFN-α) VERSIONS FOR ANTIVIRAL THERAPY**

Sofia Ines Giorgetti (1, 2), Sonia Ricotti (2), Eduardo Mufarrege (1, 2), Marina Etcheverrigaray (1, 2), Anne Degroot (3)
(1) Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET). (2) Laboratorio de Cultivos Celulares, FBCB, UNL, Santa Fe, Argentina. (3) EpiVax, Inc., Providence, RI, USA; Institute for Immunology and Informatics, University of Rhode Island, RI, USA.

rhIFN-α is widely used for the treatment of viral diseases such as chronic Hepatitis B and C (CHC). Although rhIFN-α is a "self" derived protein therapeutic, anti-IFN-α immune responses have been reported in treated patients.

Previously, we used an *in silico* approach to identify immunodominant T-cell epitopes in a hyperglycosylated IFN-alpha2b (4N-IFN) and to modify them so as to generate functional de-immunized variants. Two functional 4N-IFN variants were successfully produced in CHO cells and designated as 4N-IFN(VAR1) and 4N-IFN(VAR3). These de-immunized 4N-IFN variants had significantly reduced *ex vivo* immunogenicity in human PBMC samples.

In this work we deepen our analysis comparing the immunogenicity of these proteins in transgenic mice. After subcutaneous injection, we isolated blood and serum and quantified binding and neutralizing antibody titers by ELISA and antiviral activity assays. Interestingly, no differences in binding antibody titers were detected in serum from mice inoculated with 4N-IFN, 4N-IFN(VAR1) and 4N-IFN(VAR3) ($p \leq 0.05$). However, marked reductions in neutralizing antibody titers were observed for the de-immunized variants, highlighting the success of the de-immunization process.

Along with immunogenicity, protein stability constitutes a major concern in biotherapeutic manufacturing processes. For this, we characterized the *in vitro* protein stability of the new 4N-IFN variants against a heat treatment ranging from 25 °C to 95 °C. Both de-immunized variants exhibited enhanced stability ($p \leq 0.05$) in comparison with a commercial non-glycosylated protein, highlighting an additional advantage of these muteins.

To summarize, the functional de-immunized 4N-IFN proteins exhibit significantly reduced *in vivo* immunogenicity in transgenic mice and increased *in vitro* thermal stability when compared with a commercial nonglycosylated protein and the original molecule.

Keywords: Interferon alpha, in vivo immunogenicity, thermal stability, hepatitis therapy.

(569) **IMPACT OF IMT504 ON THE IMMUNE SYSTEM OF FEMALE NON-OBESE DIABETIC (NOD/Ltj) MICE**

Stefania Bianchi, Veronica Martinez Allo, Carlos Libertun, Marta Toscano, Victoria Lux-Lantos, Maria Silvia Bianchi
Institute of Biology and Experimental Medicine

Immunomodulatory oligonucleotide IMT504 (IMT) improved glycemia, beta cell function, and reduced leukocyte islet infiltration in spontaneous autoimmune diabetic mice (female NOD/Ltj). We analyzed the effects of IMT on immune parameters. Female diabetic NOD/LtJ mice (two consecutive glycemia levels (Gly) ≥ 250 mg/dl) were treated daily with IMT for five days (20mg/kg/day) or saline as control (DC). The day following the last injection, fasted Gly was measured and mice were sacrificed. Pancreatic leukocytes and splenocytes were obtained, immune cell populations (by flow cytometry) and cytokines expression (by q PCR) were analyzed respectively. DC mice showed 11% (2/19) spontaneous reversion of the diabetic condition whereas IMT treatment improved Gly in 72% of mice (13/18) (χ^2: DC vs IMT20: $p<0.01$). IMT treatment significantly diminished Gly at day 6 [(mg/dl): IMT20: Day 1: 307.92±34.7 vs Day 6: 230.08±97.6, $p<0.001$]. Pancreas CD45+ leukocytes showed a near significant reduction in IMT vs DC [DC CD45+%: 8.4± 5.9 vs IMT CD45+%: 3.83±2.14, $p=0.06$]. CD4+, CD8+, B220+, Cd11c+, F4/80+ and FOXP3+ population did not show significant differences. With IMT treatment, spleen IL12p40 expression showed a significant increase [DC: 1.27±0.18 vs IMT: 3.91±1.26, $p<0.01$]; while TNF-alpha expression showed a near significant decrease [DC: 1.33±0.52 vs IMT: 0.81±0.51, $p=0.07$]. IFN-gamma, IL4, and IL10 did not show significant differences. These results confirm that IMT reduced leukocyte pancreas infiltration shown by a near significant reduction in CD45+ population. Increased IL12p40 subunit is shared by both IL12 and IL23 cytokyne. IL23 promotes IL17 secretion, which could have regulatory effects, considering its inhibition on the apoptosis on suppressor myeloid cells. These results encourage further investigation on these cytokines expression (IL23 and IL17), and confirm that IMT modulates the immune system in NOD/Ltj mice.

(CONICET, UBA, ANPCYT, Fund. Williams, Fund. René Barón).
Keywords: Diabetes, Immune-System, Oligonucleotide

(721) **EXOSOMES ISOLATED FROM ASCITES OF T-CELL LYMPHOMA-BEARING MICE INDUCE A TUMOR-SPECIFIC IMMUNE RESPONSE**

Florencia Menay (1, 2), Federico Cocozza (1), Rodrigo Tsacalian (1), Analía Elisei (2), Leticia Herschlik (1), Julieta De Toro (1), María José Gravisaco (2), María Paula Di Sciullo (1), Alejandrina Vendrell (1), Claudia Waldner (1), Claudia Mongini (1, 2)
(1) Centros de Estudios Farmacológicos y Botánicos (CEFYBO). (2) Instituto Nacional de Tecnología Agropecuaria (INTA).

Exosomes are endosome-derived nanovesicles involved in cell–cell communication. Tumor exosomes can either activate or inhibit the immune system. The neoplastic stage and microenvironment can affect the quantity and composition of EVs determining their biological behavior. In this work, we have evaluated the ability of exosomes isolated from ascites of a murine T-cell lymphoma (ExoA) to modulate a tumor-specific immune response.

ExoA induced *in vitro* proliferation of tumor sensitized splenocytes when compared with unstimulated control ($p<0,001$), detected by CFSE dilution. In addition, ExoA stimulated the specific proliferation of CD4+ cells (15%) and CD8+ (3%) when compared to unstimulated sensitized splenocytes (5% and 2%, respectively). In addition, IFN-γ levels after *in vitro* stimulation with ExoA were significantly higher than unstimulated controls ($p<0,001$).

Immunization with ExoA induced both humoral and cellular immune responses that allowed the rejection of the tumor. Approximately 60% of mice immunized and challenged with LBC cells did not developed the tumor, whereas 100% control mice died 22 days following the challenge. Furthermore, the immunization induced immune memory as it also protected mice against a second challenge with LBC cells. However, it had no effect on a non-related mammary adenocarcinoma, demonstrating that the immune response elicited was specific. Intracellular staining

revealed that IFN-γ secreting CD4+ and CD8+ cells from ExoA-immunized mice were significantly higher in immunized individuals ($p<0,01$), showing that a TH1 response is involved in tumor rejection. Our findings confirm exosomes as promising defined acellular tumor antigens for the development of an antitumor vaccine.

Keywords: exosomes, T-cell lymphoma, immune response, tumor vaccine, ascites