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REUNIÓN CONJUNTA SAIC SAFIS ALACF 2024

LXIX REUNIÓN ANUAL DE LA
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(SAIC)

XXVI SOCIEDAD ARGENTINA DE FISIOLOGÍA
(SAFIS)

ASOCIACIÓN LATINOAMERICANA DE CIENCIAS FISIOLÓGICAS
(ALACF)

19-22 de noviembre de 2024
Usina del Arte – Ciudad Autónoma de Buenos Aires

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RAC1 is a small GTPase that plays a crucial role in regulating various cellular processes. Its hyperactivation has been implicated as a key mediator of epidermal dysfunction, cell hyperproliferation and inflammatory disorders, such as psoriasis and atopic dermatitis (AD). In this study, we evaluated 1A-116, a RAC1 inhibitor initially developed as an antitumor agent, now being investigated for the first time as a topical therapeutic aimed at targeting the aberrant activation of RAC1 in a range of skin conditions. *In vitro* studies using HaCaT (human keratinocytes) and HDF (dermal fibroblasts) to assess the effects of 1A-116 on cell viability were conducted. Treatment with 1A-116 resulted in a significant reduction in cell viability ($P < 0.05$) in both cell lines, without inducing skin corrosion or irritation, as confirmed by EpiSkin™ Small Model SCT. Additionally, 1A-116 significantly decreased total reactive oxygen species (ROS) production ($P < 0.05$) and inhibited the secretion of pro-inflammatory cytokines, including IL-6, IL-1β, IL-17A, IL-4, and TNF-α. To further assess the skin penetrability of 1A-116, *ex vivo* testing was performed using human skin tissue showing a good skin penetrability profile. Additionally, two *in vivo* models were established to evaluate the efficacy of 1A-116. An atopic dermatitis (AD) model was used to assess the activity of 1A-116, showing a significant anti-inflammatory effect *in vivo* and the reduction in pro-inflammatory cytokines expression as seen *in vitro*. Furthermore, using a psoriasis-like dermatitis model we evaluated different topical formulations of the compound, observing that the ointment formulation of 1A-116 significantly reduces epidermal thickness. The comprehensive evaluation of 1A-116 across multiple models underscores its potential as a therapeutic agent for skin disorders driven by RAC1 hyperactivation. These findings pave the way for further research into the efficacy of 1A-116 in treating inflammatory skin conditions.

173. 316 **IgY TECHNOLOGY - AN ALTERNATIVE METHOD FOR THE PRODUCTION OF OPHIDIAN ANTIVENOM AGAINST *CROTALUS DURISSUS TERRIFICUS* (ARGENTINEAN RATTLESNAKE)**

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Snakebite envenoming is caused by the injection of a mixture of toxins, and represents an example of a pathology whose effective treatment is the administration of antivenoms based on sera or plasma from hyperimmunised large animals (horses). An alternative to mammalian polyclonal sera is the use of egg yolk antibodies because of their advantages in terms of animal welfare and lower production cost. The aim of this study is to produce an IgY antivenom against *Crotalus durissus terrificus* venom on a pilot scale, using more simplified purification methods. A group of laying hens (n=2) was immunised i.m. with 80 µg of whole *C. d. terrificus* venom (pool) 9 times on days 0, 14, 28, 71, 237, 289, 304, 473 and 487. For the first immunisation, the venom was emulsified with complete Freund's adjuvant (1st injection) and incomplete for boosters. Eggs were collected for 10 days after the 7th, 8th and 9th immunisation. To choose the optimal purification method, different protocols were evaluated: precipitation with ammonium sulphate (24 and 26% w/v), PEG-6000 (12% w/v) and caprylic acid (7% v/v). Thimerosal 0.01% (w/v) was added for preservation. The mean effective dose (ED50) was assessed in NIH mice by mixing 3 mean lethal dose (LD50) of the venom with increasing volumes of IgY antivenom according to World Health Organization guidelines. The optimal LD50 was obtained by precipitation with ammonium sulphate instead of using PEG-8000 and caprylic acid. After 9 immunisations, 1 ml of IgY antivenom purified using PEG-8000 neutralised 158 µg of venom. In addition, 1 ml of IgY antivenom purified by caprylic acid neutralised < 40 µg of venom. However, 1 ml of IgY antivenom purified by ammonium sulphate neutralised 395 µg of venom. In conclusion, immunisation of hens with sublethal doses of *C. d. terrificus* venom produced an antivenom with ED50 similar to those obtained in horses and could be an alternative production method. The IgY technology may enable the production of effective and affordable antivenoms.

174. 361 **EPIDEMIOLOGY OF AA AMYLOIDOSIS COHORT STUDY. DIFFERENCES IN THE LATENCY PERIOD FROM THE DIAGNOSIS OF THE INFLAMMATORY CONDITION TO THE DIAGNOSIS OF AA AMYLOIDOSIS**

María Adela Aguirre[1,2], Elsa Mercedes Nucifora[3], Marcelina Carretero[4], María Soledad Sáez[5], Patricia Beatriz Sorroche[5], María Lourdes Posadas Martínez[4,2]
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Introduction: Amyloidosis is characterized by the deposition of positive Congo Red material. AA amyloidosis is associated with infectious, autoimmune, or idiopathic inflammation. The time from diagnosis of inflammation to diagnosis of amyloidosis is named latency. The importance of knowing the latency period, allows early suspicion of the entity and detection of risk factors for the development of amyloidosis. **Objective:** to estimate latency period from the diagnosis of the inflammatory condition to the diagnosis of AA amyloidosis in patients at Hospital Italiano de Buenos Aires from 01/01/2012 to 10/31/2019 and characterize these patients. **Methods:** A prospective cohort of adults with AA amyloidosis was designed in the Institutional Registry of Amyloidosis of Hospital Italiano de Buenos Aires. Enrollment was based on tissue AA confirmation. Information was collected on demographic characteristics, characteristics at diagnosis, characteristics of the underlying disease, treatment, and prognosis. **Results:** Idiopathic forms reached 56% (n=13). The underlying diseases were autoimmune in 26% (n=6) and infectious in 17% (n=4). The median latency period was 20 years [interquartile range (IQR 1-32)], being 30 years (IQR 12-35) for autoimmune and 5 years (IQR 5-19) for infectious diseases. The main organic involvement was renal (87%). The treatment rate was 65%. During follow-up the overall mortality rate was 17% (confidence interval 95% 6-40%). **Conclusion:** The latency period was lower for infectious diseases than for autoimmune diseases in this cohort. Treatment of infections could prevent the development of kidney failure in this group of patients. Knowing the distribution of causes of AA amyloidosis and characteristics in our region is important and has a healthcare impact. As with rare diseases, the suspicion of amyloidosis is low. Dissemination of local data could help with early diagnosis.

175. 488 **ZFP-36 PROTEINS IN MONOCYTE AND MACROPHAGE INFLAMMATORY SIGNALING AND DIFFERENTIATION. MODELLING THEIR POST-TRANSLATIONAL MODIFICATIONS, INTRACELLULAR LOCATIONS, INTERACTOME, STRUCTURAL HETEROGENEITY AND HALF-LIFE**

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1 ICL and MRC UK, 2 ICGEB Italy, 3 CONICET Argentina, 4 RTI Health Solutions, 5 GSK Asia

ZFP36 and ZFP36L1 (L1) are RNA-binding nucleo-cytoplasmic

phospho-proteins with zinc-fingers, modulating the decay of AU-rich mRNAs such as those of some inflammatory cytokines. Their individual roles or redundancy in macrophages are unknown. Both are post-translationally modified with multi-site phosphorylation by many kinases and by other PTMs. The impact of all PTMs on their roles, location, mRNA binding, folding, modification code, half-life and interactions are understudied. We aimed to study them in THP1 and HeLa cell lines by subcellular fractionation, immunoprecipitation, immunoblotting, far-WB, dye binding, transfection, radiolabeling and 1D/2D gels, also using enzyme inhibitors and TLR ligands for cell treatments. We studied rZFP36 mutants by kinase assays and ZFP36 by informatic, interactome and MS analysis. As novel PTM, we considered the isomerization in proline-directed phosphosites. By densitometry of their isoforms in gels, results suggested with statistical significance that the hyperphosphorylated forms of L1 and ZFP36 were cytoplasmic but insoluble, interacting with the cytoskeleton. Thus, both distribute in at least 6 locations: cytosol, cytoskeleton, mRNAs, stress-granules, P-bodies and nucleus. Besides, both cellular and rZFP36 isomerize. ZFP36 becomes a model for multi-site phosphorylation and isomerization. L1 levels were different in monocytic and macrophage states, suggesting a role in a differentiation switch but not in inflammation. ZFP36 was affected by inflammatory signaling but not by macrophage adherence or multinucleation or ribotoxic stress. We visualize a complex rheostatic regulation in which ZFP36 is controlled by interactions with ions, proteins, mRNAs and proteasomes, behaving as a polyanion with electrostatic interactions and disordered regions that can isomerize. More studies are needed to understand their molecular heterogeneity and if they will become drug targets, to fine-tune their many activities without side effects

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176. 030 **DEVELOPMENT OF MIXED MICELLAR SYSTEMS AS IMMUNOSTIMULANT NANOPLATFORM FOR NOVEL SUBUNIT VACCINE FORMULATIONS**

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The use of nanoparticulate systems as adjuvants has gained considerable strength, enhancing the efficacy and safety of subunit vaccines. Polymeric micelles (PMs) based on polyoxyethylene (PEO) and polyoxypropylene (PPO) tri-block copolymers represent a promising nanoplatform for immunostimulant delivery. QS-21, a saponin fraction from *Quillaja saponaria*, is encapsulated within the AS01 adjuvant system in FDA-approved vaccines to boost immunogenicity and reduce hemotoxicity, though it remains a costly lipid-based platform. Our aim is to develop mixed PMs based on block copolymers (P123) and QS-21 as a novel immunostimulant nanoplatform (P123/QS-21), characterize their physicochemical properties, evaluate *in vitro* hemotoxicity and *in vivo* immune response. The P123/QS-21 system was prepared by hydrating its components in PBS at 4°C overnight. Key assembly parameters, including hydrodynamic diameter (D_h), polydispersity index (PDI), and critical micellar concentration (CMC), were determined using dynamic light scattering (DLS). Hemolytic activity was assessed, and the immune response was measured by antibody titers in blood serum and bronchoalveolar lavage (BAL), along with neutralizing antibodies in serum after intramuscular immunization with the SARS-CoV-2 Spike recombinant protein (provided by NANOBIOTEC) formulated with P123/QS-21. The P123/QS-21 system demonstrated effective micellar assembly, with a D_h under 25 nm, PDI < 0.1, and a CMC value intermediate between those of P123 and free QS-21, indicating the formation of a new entity. This formulation showed reduced hemolytic activity compared to free QS-21, and achieved a two-fold increase in anti-Spike antibody titers in serum and a ten-fold increase in BAL. Notably, anti-Spike neutralizing activity was also observed. These findings represent a step forward in the development of novel and cost-effective nanoparticulate adjuvants for subunit vaccine formulations.

177. 098 **ENHANCED RADIOSENSITIZATION OF MELANOMA CELLS BY GOLD NANOPARTICLES AND POLYMERIC MICELLES COMBINED WITH DOXYCYCLINE**

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Gold nanoparticles (AuNPs) were synthesized using polyoxyethylene (PEO) and polyoxypropylene (PPO) block copolymers (F127, F68, P85) through two methods: (i) direct formation in the presence of reducing copolymers, creating AuNPs-PMs complexes, and (ii) preformed polymeric micelles (PMs) and AuNPs (by Turkevich synthesis) resulting in hybrid AuNPs/PMs blends. Doxycycline (Doxy), a mitochondrial biogenesis inhibitor which acts as an active ligand, was adsorbed onto the surface of these nanostructures. All nanosystems were characterized by UV-Visible, DLS and TEM. Hydrodynamic diameters (D_h) increased with higher copolymer molecular weights (M_W) and concentrations (%w/v): AuNPs-PMs complexes ranged from 100-150 nm (0.5-5%) to 400-500 nm (10%); while AuNPs/PMs blends were slightly smaller, ranging from 20-60 nm (0.5-5%) to 500 nm (10%). P85 (lowest M_W) displayed the smallest D_h (under 100 nm). All structures remained stable for 20 days. Copolymers prevented spontaneous AuNPs aggregation in presence of Doxy. Neither AuNPs (2.5-50μM), nor F127 and F68 PMs (0.1-1%) and their respective complexes and blends had a significantly impact on cell metabolic activity in A375 (radiosensitive) and Mel-J (radiresistant) melanoma cells. In contrast, free Doxy decreased melanoma cell viability below 75% at concentrations higher than 25μM, reaching 14-16% of viability at concentrations of ~1mM, while Doxy (25μM) combined complexes and blends displayed a mayor reduction in cell viability (<60%), for both A375 and Mel-J. Radiosensitization was initially studied by irradiating cells with gamma rays (2Gy, 137Cs), where cells pretreated with Doxy-combined complexes and blends showed a presumptive reduction in viability. Further clonogenic assays are underway to better understand this effect. The combination of Doxy with these nanostructures may offer a novel strategy to enhance radiotherapy efficacy in resistant melanoma.

178. 111 **CORNEAL ENDOTHELIAL DIFFERENTIATION OF HUMAN AMNIOTIC MESENCHYMAL STEM CELLS**

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