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SOCIEDAD ARGENTINA DE INVESTIGACIÓN CLÍNICA (SAIC)

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RESPONSIBLE EDITORS
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NANOBODIES WITH NEUTRALIZING PROPERTIES AGAINST SARS-COV-2 VIRUS AS PROMISING MOLECULES FOR COVID-19 TREATMENT

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The COVID-19 disease caused by the coronavirus SARS-CoV-2 is the major outbreak in the last decades. Several vaccines have been approved to prevent the disease, however therapeutic and prophylactic molecules than can mitigate its symptoms, especially in cases where vaccines are ineffective or contraindicated, are still a necessity. The virus can infect cells through the interaction of the receptor-binding domain (RBD) of its S protein with the angiotensin converting enzyme 2 (ACE2) receptor. Consequently, the S protein has become the principal target for therapeutic interventions. Llama-derived single domain antibodies or Nanobodies (Nbs) are small molecules with extraordinary affinity for different targets that can be produced at low cost. In this work we present results showing the neutralizing capacity of Nbs directed against the S protein, both *in vitro* and *in vivo*.

A llama was immunized with the pre-fusion and locked S and RBD proteins expressed in HEK-293T cells. Once high antibody titers were obtained, an Nb library was generated. More than 80 Nbs clones against S and RBD proteins were selected by phage display, 52 of them with unique sequences were expressed in *Escherichia coli* WK6 and purified by immobilized metal chelate chromatography, followed by size exclusion chromatography. Ten of those Nbs were able to prevent the transduction of pseudovirus expressing SARS-CoV-2 S protein as well as the infection of Vero cells with the wild-type SARS-CoV-2 virus strains circulating both in Argentina and in the United States of America. Preliminary results have shown that at least 3 of those Nbs are capable of neutralizing the SARS-CoV-2 isolate USAWA1/2020 in a mouse model, with protection ranging from 60 to 80% after a lethal challenge.

In conclusion, we have selected several Nbs capable of neutralizing the SARS-CoV-2 virus. The strong neutralizing activity of some of these molecules makes them potential candidates for intranasal treatment of COVID-19.

ANTIANDROGENS POSE A PROTECTIVE EFFECT AGAINST COVID-19 BY BOOSTING THE HUMAN MYXOVIRUS RESISTANCE GENE 1 (MX1)

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Population-based studies have shown that prostate cancer (PCa) patients undergoing androgen-deprivation therapies (ADT) were partially protected from COVID-19. Men treated with proxalutamide in a recent clinical trial, showed reduced COVID-19 hospitalization rate. In this work we assessed gene expression profiles and androgen regulation of the main host cell receptors described for SARS-CoV-2 and potential antiviral genes involved in response to coronavirus infection.

Multiple bioinformatics analyses were performed to study host cell receptors and antiviral proteins in SARS-CoV-2 infection and the gene expression changes upon ADT was assessed. We used publicly available datasets from: a) SARS-CoV-2 positive and negative patients' nasopharyngeal swabs at time of diagnosis (GSE152075, n=453), b) SARS-CoV-2 infected human cell lines and ferrets (GSE1407507),

c) ChIP-seq experiments evaluating androgen receptor binding (GSE66037, GSE28950, GSE108704).
Results showed that SARS-CoV-2 positive cases had higher *MX1* expression, and multivariable regression showed that *MX1* expression significantly increased with viral load. Also, *MX1* was significantly up-regulated in tracheal samples from ferrets intranasally infected with SARS-CoV-2. Similar results were found in A549 and Calu3 lung cell lines. Since ADT might result in a therapeutic advantage against COVID-19, we next evaluated *MX1* regulation by dihydrotestosterone (DHT). First, comparable *MX1* levels in lung, prostate and salivary gland of healthy humans were observed (GTEx). LNCaP cells treated with DHT showed a decrease ($p<0.05$) in *MX1* mRNA levels. ChIP-seq experiments showcased AR binding sites on the *MX1* sequence upon DHT. Further, comparison of paired PCa patient's samples before and after ADT showed *MX1* upregulation ($p<0.05$) after ADT.
In summary, *MX1* raises as a critical responder in SARS-CoV-2 infection and we demonstrate *MX1* modulation by DHT. We propose *MX1* as a key player in the therapeutic advantage posed by ADT.

THE OTHER SIDE OF COVID-19 PANDEMIC: EFFECTS ON FEMALE FERTILITY

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SARS-CoV-2 invades the target cell by binding to angiotensin converting enzyme 2 (ACE-2). In the human ovary, ACE-2 is expressed in stromal and granulosa cells.
Our objective was to evaluate the effect of SARS-CoV-2 infection on female gonad.
FF (follicular fluid) from patients undergoing ART (n= 80; 21–41 years old; November 2020-April 2021) were divided in two groups: FF from control patients and FF from recovered COVID-19 patients (asymptomatic and with mild symptoms). The levels of IgG antibodies against SARS-CoV-2, IL-1β, IL-10 and VEGF were measured in FF by ELISA.
Using a granulosa cell line (COV434) and an endothelial cell line (EA.hy926), we studied the effect of FF from control and recovered COVID-19 patients. The expression of StAR, ERα and ERβ, 3β-HSD, VEGF, ANGPTs (angiogenesis-related proteins) and γH2AX (DNA damage marker) was evaluated by WB. Proliferation was evaluated by a WST-1 assay. Endothelial cell migration was evaluated by a wound healing assay. We performed Student's t test or one-way ANOVA.
The results showed that 91.3% of post-COVID-19 FF was positive for IgG against SARS-CoV-2. Patients with higher levels of SARS-CoV-2 IgG showed a decrease in the number of retrieved oocytes ($p<0.05$). The levels of VEGF and IL-1β were lower ($p<0.05$) in post-COVID-19 FF, while IL-10 did not differ.
In COV434 cells with post-COVID-19 FF, the expression of StAR, Erβ and VEGF was decreased ($p<0.05$), while ERα and 3β-HSD did not change.
In EA.hy926 cells with post-COVID-19 FF, a decrease in cell migration was observed ($p<0.0001$) without changes in the expression of ANGPTs. Both cell types showed higher expression of γH2AX with post-COVID-19 FF ($p<0.05$). No differences were found in COV434 and EA.hy926 cell proliferation rates between the groups.
In conclusion, these results describe that SARS-CoV-2 infection alters the follicular microenvironment, damaging ovarian function, and affecting reproductive performance in recovered COVID-19 patients.
This project that involves the use of human samples from assisted fertilization techniques has been approved by the IByME Ethics Committee in 2020 (REGISTRATION CODE 2850, October 2020).
This project was carried out between January and June 2021.

SAIC – REPETTO AWARD

Juries: Dr. Eduardo Cuestas, Dra. Paula Dominguez y Dr. Ramón Exeni

EARLY ANTIPARASITIC TREATMENT PREVENTS PROGRESSION OF CHAGAS DISEASE: RESULTS OF A LONG-TERM CARDIOLOGICAL FOLLOW-UP STUDY IN A PEDIATRIC POPULATION

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Objective: To evaluate cardiac involvement in children after pharmacological treatment for Chagas disease (CD).

Methods: A descriptive study of a cohort of pediatric CD patients treated with benznidazole (Bz) or nifurtimox