PHARMACOGENETICS RESEARCH AND TESTING AT INSTITUTO NACIONAL DE CÁNCER, BRAZIL

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The implementation, current status and perspectives of a pharmacogenomic (PGx) program at the Brazilian National Cancer Institute (INCA), targeting the cancer chemotherapeutic drugs – fluoropyrimidines, irinotecan and thiopurines will be presented. This initiative was designed as a research project, approved by the institutional review board. A dedicated task force developed standard operational procedures, which were successfully applied to test gastrointestinal cancer INCA outpatients and pediatric patients from INCA and seven other hospitals, diagnosed with acute lymphoblastic leukemia. The program has been subsequently expanded to include gastrointestinal cancer patients from two additional cancer treatment centers. We anticipate implementation of routine pre-emptive PGx testing at INCA but acknowledge challenges associated with this transition, such as continuous financing support, availability of trained personnel, adoption of the PGx-informed prescription by the clinical staff and, ultimately, evidence of cost–effectiveness.

SIMPOSIO SAI N°1: COVID-19 IN PREGNANCY, CHILDHOOD AND AGING

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C): IMMUNE DYSREGULATION AND CORRELATES OF DISEASE SEVERITY

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Multisystem inflammatory syndrome in children (MIS-C) is a life-threatening post-infectious complication occurring unpredictably weeks after mild or asymptomatic SARS-CoV-2 infection. We profiled MIS-C, adult COVID-19, and healthy pediatric and adult individuals using single-cell RNA sequencing, flow cytometry, antigen receptor repertoire analysis, and unbiased serum proteomics, which collectively identified a signature in MIS-C patients that correlated with disease severity. Despite having no evidence of active infection, MIS-C patients had elevated S100A-family alarmins and decreased antigen presentation signatures, indicative of myeloid dysfunction. MIS-C patients showed elevated expression of cytotoxicity genes in NK and CD8+ T cells and expansion of specific IgG-expressing plasmablasts. Clinically severe MIS-C patients displayed skewed memory T cell TCR repertoires with expansion of *TRBV11-2*+ T cells and autoimmunity characterized by endothelium-reactive IgG. The alarmin, cytotoxicity, TCR repertoire, and plasmablast signatures we defined have potential for application in the clinic to better diagnose and potentially predict disease severity early in the course of MIS-C.
Ramaswamy et al., 2021, *Immunity* 54, 1–13

TISSUE RESIDENT CD4+T CELLS IN COVID-19 PATIENTS

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abstract not available

COVID-19 IN CHILDREN- AN EVOLVING PICTURE

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Among the most intriguing observations in Coronavirus disease 2019 (COVID-19) are the reduced incidence and mortality rates in children. In fact, and in contrast to other viral respiratory infections such as those caused by influenza and respiratory syncytial viruses, SARS-CoV-2 usually develops as a mild infection in children. The reasons for this remain unclear. Considering that pulmonary infiltration by neutrophils plays a relevant role in the development of severe COVID-19 in adults, we analyzed whether neutrophils in children infected with SARS-CoV-2 expressed a particular phenotypic profile. We found that neutrophils from children with COVID-19 had a distinct signature characterized by a reduced expression of adhesion molecules involved in neutrophil migration together with an increased expression of both, the inflammatory markers CD64, HLA-DR and PECAM-1 and the inhibitory receptors leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1) and programmed death-ligand 1 (PD-L1). This finding is unusual as neutrophil activation is associated with the up-regulation of ad-

hesion molecules as observed in adults with COVID-19. We hypothesized that this particular signature might prevent neutrophil infiltration in the pulmonary capillaries thus providing protection against tissue injury in children. While the course of SARS-CoV-2 infection in children is usually mild, some children develop severe COVID-19. It has been shown that a severe disease in adults is linked to a delayed kinetic of antibody production. We also studied whether a defective antibody response could be associated with a more severe condition in children. We found that children with severe COVID-19 display a very poor and late antibody response against SARS-CoV-2. This weak antibody response occurs due to a low frequency of circulating Follicular Helper T cells and a systemic inflammatory response revealed by high levels of inflammatory cytokines in plasma.
Vaccines against COVID-19 have shown very high levels of safety and effectiveness. In countries where vaccination was widely performed, such as in Israel and the United Kingdom, the infection rate in children is worsening. In this scenario, it is urgent to characterize the factors determining the predisposition of some children to suffer severe COVID-19.

COVID-19 AND PREGNANCY

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abstract not available

SIMPOSIO SAIC N°1: GENERATION AND INTEGRATION OF NEURAL STEM CELLS IN SYNAPTIC CIRCUITS: IMPORTANCE IN NEUROLOGICAL DISORDERS

LRIG1 CONTROLS NEURAL STEM CELL HOMEOSTASIS IN THE DEVELOPING CORTEX

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The cell-intrinsic mechanisms underlying the decision of a stem/progenitor cell to either self-renew or differentiate are incompletely understood. Here, we show that Lrig1 is early expressed in the neocortex during the period of cortical neurogenesis. The majority of the progenitor cells expressing high levels of Lrig1 were negative for the proliferative marker Ki67, indicating that Lrig1 expression is inversely correlated with proliferation. In agreement with this, we show that Lrig1 abrogates the self–renewing activity of cortical neural progenitor cells induced by mitogenic signals. Cortical progenitors derived from Lrig1-deficient mice give rise to an increased number and size of mitogen-induced neurospheres. Analysis of Lrig1-deficient mice also shows a significant increase in the number of cycling cells during cortical development in vivo. Notably, Lrig1 restricts proliferation of NPCs by regulating the expression levels of cyclins and cell-cycle inhibitors. Together, our results indicate that Lrig1 deficiency triggers proliferation of cortical precursor cells and suggest that Lrig1 may promote neural stem cell quiescence.

DENDRITIC REMODELING AND SYNAPTIC INTEGRATION OF ADULT-BORN HIPPOCAMPAL NEURONS

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In the mammalian adult hippocampus, new neurons are continuously generated throughout life in the subgranular zone of the dentate gyrus. Increasing evidence point out the contribution of adult-born hippocampal granule cells (GCs) to cognitive processes such as learning and memory, indicating the relevance of understanding the molecular mechanisms that control the development of these new neurons in the preexisting hippocampal circuits. Cell proliferation and functional integration of adult-born GCs is a process highly regulated by different intrinsic and extrinsic factors. In this work, we described a novel role of the Glial Derived Neurotrophic Factor, GDNF, acting through its GFRα1 receptor in the control of dendritic structure and spine density of adult-born granule cells. Our findings reveals that GFRα1 is required for the integration of the new born neurons into preexisting circuits and for spatial memory processing.