therapeutic role in the COVID 19 pandemic. This multifactorial profile is unique to melatonin and is not shared by any other therapeutic drug candidate in the COVID 19 pandemic. Controlled studies are urgently needed to support this proposal.

## CONFERENCIA INAUGURAL

### IMMUNE CHECKPOINT BLOCKADE IN CANCER THERAPY: NEW INSIGHTS INTO THERAPEUTIC MECHANISMS

**James P. Allison, Ph.D. - Premio Nobel de Fisiología / Medicina 2018**
*MD Anderson Cancer Center, Houston, USA.*

Since the finding that CTLA-4 is an immune checkpoint which inhibits T cell proliferation, the existence of multiple non-redundant pathways that limit T cell responses, including the PD-1/PD-L1 axis, has been shown. Ipilimumab, a checkpoint inhibitor antibody to CTLA-4 that blocks its interaction with B7 molecules on the surface of antigen presenting cells and prohibits T cell co-activation, provides long-term survival benefit in ~20% of late stage melanoma patients. Many patients appear cancer-free after a decade or more. PD-1/PD-L1 antagonist antibodies provide objective responses against several tumor types with response rates of about ~25%. Combination of anti-PD-1 and anti-CTLA-4 increases the response rate to ~50% in late stage melanoma and is now standard of care. The FDA has now approved at least 7 different checkpoint antibodies for a variety of cancers. Still, checkpoint inhibitors have yet to provide benefit to patients with immunologically cold tumors. Additionally, potentially severe immune adverse events limit their use in lower mutational burden cancers that often arise later in life. More recent work in my lab and the Immunotherapy Platform centers on CyTOF and single cell RNAseq profiling of tumor-infiltrating T cell populations that mediate effective responses to current immune monotherapies and combinations. The results of this work provide an avenue to identify rational combination therapies that could prove effective for patients and cancers that currently do not respond to immunotherapy while ameliorating potential side effects of increased immune activity.

## CONFERENCIA PLENARIA ALFREDO LANARI

### IRON METABOLISM IN OLIGODENDROCYTES AND ASTROCYTES: FRIEND OR FOE?

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Recent reports show that astrocytes (AST) are able to create a permissive environment for remyelination through their action on oligodendrocyte (OLG) precursor migration, proliferation, and differentiation. When disrupted, iron homeostasis negatively impacts OLG differentiation and impairs myelination. We demonstrate that iron deficiency (ID) affects not only OLG maturation but also AST.

Using gestational iron deprivation, we studied OLG requirements for their progression to a mature myelinating state and energy metabolism in primary cultures of OLG and AST from newly born control and ID pups. In particular, oxygen consumption and extracellular acidification rates were measured using a Seahorse extracellular flux analyzer. Both ID AST and OLG exhibited decreased spare respiratory capacity, which indicates that maternal ID effectively induces mitochondrial dysfunction. Absence of glycogen granules was observed in ID AST and an increase in ROS production was detected in ID OLG. Mitochondrial fission was increased in ID AST, while fusion was prevalent in ID OLG. Electron microscopy also showed abnormal cristae in ID mitochondria in OLG as well as in AST. These findings further prove that the regulation of cell metabolism may impact cell fate decisions and maturation.

An additional model of ID was developed by knocking down the divalent metal transporter 1 (DMT1), a multi-metal transporter with a primary role in iron transport and present in AST and OLG. OLG maturation was compromised in primary OPC cultures treated with conditioned medium from DMT1-silenced AST, which suggests that molecules secreted by AST may be affected.