ImmuneCar

New pathways for suppressive Immune Checkpoints inhibition

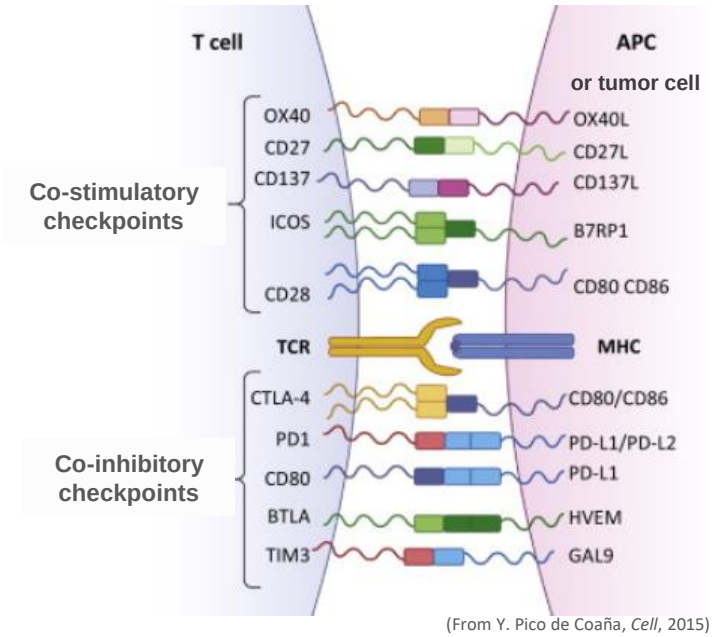
January 2019

Immune Checkpoints therapeutic potential

- Immune Checkpoints are T cell receptor co-regulators that can either stimulate or inhibit T cell mediated immune response. They play a significant role in tumor immune escape.

- Targeting co-suppressive Immune Checkpoints (ex: PD-1 and CTLA-4 antibodies therapies) improves the overall survival for patients in several cancers: melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer, Hodgkin lymphoma…

- Notably, only a small subset of patients (~25%) respond to immune checkpoint inhibitors (ICI), due to innate or acquired resistances → **need to expand the long-term clinical benefit of ICI to more patients.**



(From Y. Pico de Coaña, *Cell*, 2015)

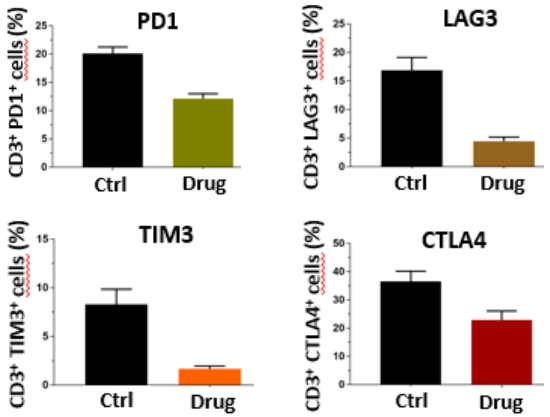
➡ **An attractive approach to improve ICI clinical effects is to target multiple co-suppressive checkpoints simultaneously.**

Targeting checkpoints expression as a new therapeutic approach

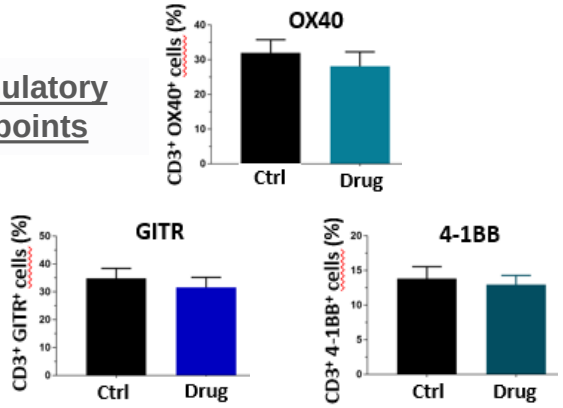
➡ **The expression of suppressive Immune Checkpoints is regulated by a specific mechanism in lymphocytes:**

- **All suppressive checkpoints can be simultaneously inhibited**.
- **Use of non specific commercially available drugs** shows that PD-1, CTLA-4, TIM-3 and LAG-3 protein levels were reduced in activated CD4 or CD8 T cells, but not those of co-stimulatory checkpoints OX40, GITR and 4-1BB.

Co-inhibitory checkpoints



Co-stimulatory checkpoints



- **Need to identify new specific inhibitors**, not impacting other cellular processes

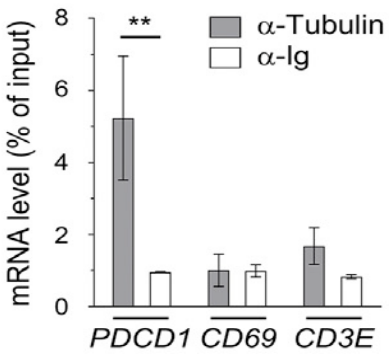
➡ **Development of a method for screening of novel co-suppressive Immune Checkpoints expression inhibitors:**

- Simple *in vitro* method, validated on non specific commercially available drugs.

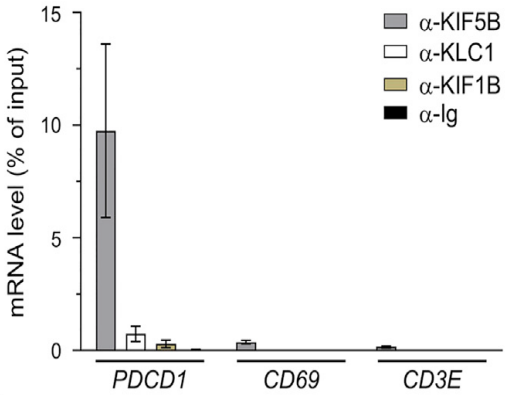
Implication of the Stress Granules in the Immune Checkpoints Expression

- mRNA granules, such as **Stress Granules** (SGs), regulate mRNA transport, stability and translation. The **microtubules cytoskeleton** is essential in the regulation of such granules.

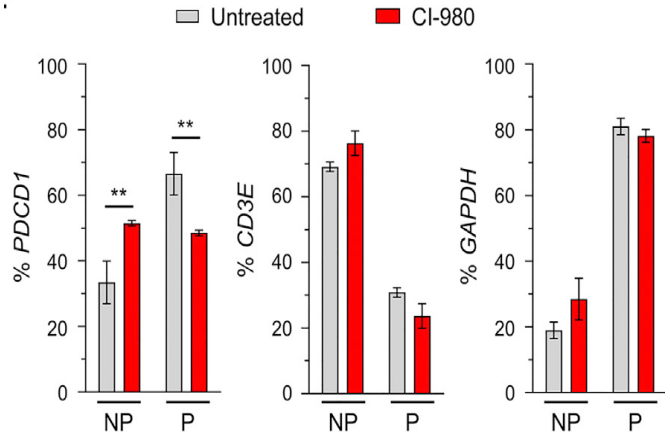
Tubulin is associated with PDCD1 mRNA in activated T Cells



Kinesin 1, via KIF5B, interacts with the PDCD1 mRNA



CI-980 shifted PDCD1 mRNA from Polysomal to Non-Polysomal fractions

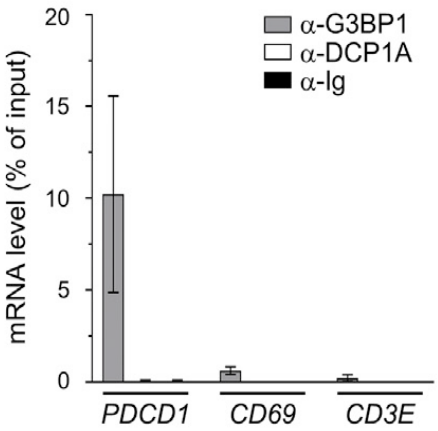


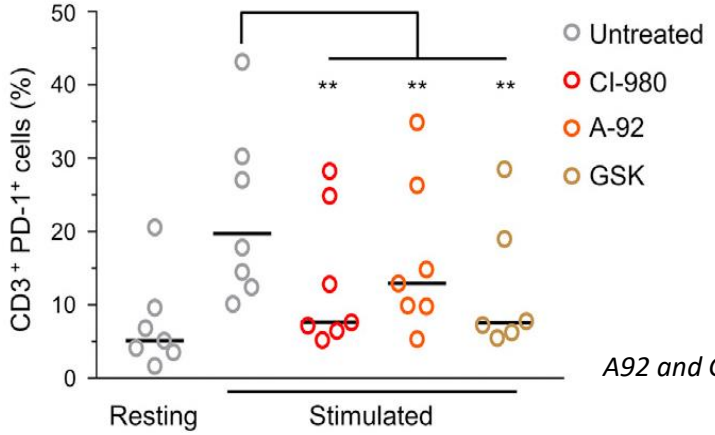
CI-980: PD1 inhibitor

➡ **Kinesin 1 is involved in the microtubule-dependent transport of the PDCD1 mRNA.**

Implication of the Stress Granules in the Immune Checkpoints Expression

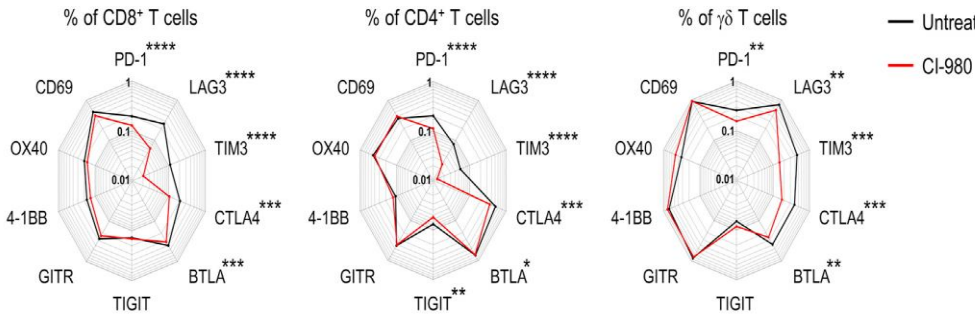
SGs interact (via G3BP1) with PD1



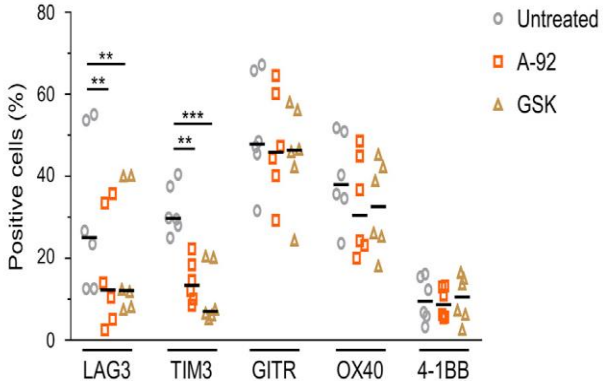


A92 and GSK = SG drugs

The expression of several inhibitory checkpoints can be controlled simultaneously



Expression of immune chekpoint receptors



➡ **PD1 Inhibitor and Stress Granules inhibitors can inhibit several checkpoint receptors.**

➡ **Stress Granules as a target to inhibit checkpoints expression.**

New drugs targeting co-inhibitory checkpoints expression

BENEFITS

- Simultaneous targeting of all co-suppressive checkpoints.
- Global inhibition making resistance mechanisms unlikely.
- Lesser development & manufacturing costs than antibody therapeutics.
- Potential use for infectious diseases.

OPPORTUNITY

- Screening novel inhibitors of suppressive checkpoints expression.
- Stress Granules as a new target to regulate immune response.

Intellectual property & information

- **Patent EP17305514 (May 2017)** filed by Inserm and Toulouse Paul Sabatier University on behalf of the Cancer Research Center of Toulouse.
- **Patent EP18306286 (October 2018)** filed by CNRS, Inserm and Toulouse Paul Sabatier University on behalf of the Cancer Research Center of Toulouse.

Inserm

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