THE ENDOGENOUS PROTEIN CIRP AS IMMUNIZATION VECTOR FOR A NEW VACCINATION PLATFORM

cima
CENTER FOR APPLIED MEDICAL RESEARCH
UNIVERSITY OF NAVARRA

- The essential role of CD8 T cells in tumor antigen recognition and elimination of malignant cells has led to the development of immunotherapeutic strategies aimed at activating these immune responses.
- Anti-tumor vaccines yielded promising results in preclinical models but they have demonstrated limited clinical efficacy. However, with the advent of new checkpoint inhibitors, vaccines are gaining new options in combination therapies.
- A proper vaccine formulation should be able to target the antigen to dendritic cells (professional antigen presenting cells) and induce their activation for efficient CD8 T cell stimulation.
- We hypothesized that certain endogenous pro-inflammatory protein CIRP may behave as an immunization protein vector, establishing a vaccination platform which confers targeting and immunostimulatory properties to those antigens covalently bound to it.
- **Indication:** Cancer and infectious pathogens

Approach

By using dendritic cells we have tested in vitro the immunostimulatory and targeting capacity of CIRP-containing vaccines. We have also studied these properties in vivo in immunization experiments, used as antitumor therapeutic vaccines. We have finally analyzed its capacity to perform in combination with checkpoint inhibiting antibodies approved for clinical use and with additional immunostimulatory adjuvants.

Key concepts and Target Identification

- CIRP induces in vitro murine DC maturation, cytokine production and enhances presentation to T cells of CIRP-bound antigens
- Antigen linkage to CIRP enhances in vivo induction of T cell responses in a type I IFN-dependent manner.
- Vaccination with CIRP-containing immunogens as stand-alone has therapeutic anti-tumor effect.
- CIRP behaves as a vaccination platform for combination with other immune enhancing strategies, such as checkpoint inhibiting antibodies and immunostimulatory adjuvants.
- CIRP induces phenotypic and functional activation of human DC.

Target Validation

- In vitro and in vivo experiments demonstrated the immunostimulatory and targeting capacity of CIRP-containing immunogens, which have antitumor effects as vaccines and can be combined with other immune enhancing strategies

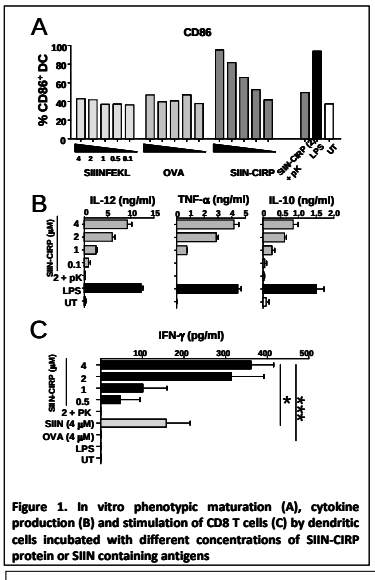

Figure 1. In vitro phenotypic maturation (A), cytokine production (B) and stimulation of CD8 T cells (C) by dendritic cells incubated with different concentrations of SIIN-CIRP protein or SIIN containing antigens

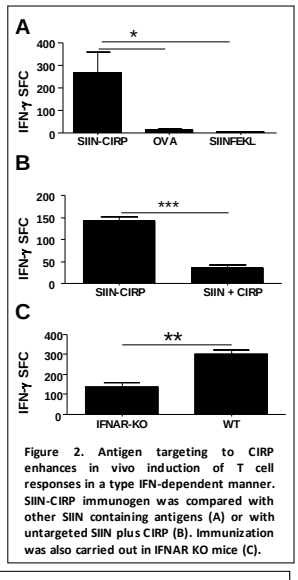

Figure 2. Antigen targeting to CIRP enhances in vivo induction of T cell responses in a type IFN-dependent manner. SIIN-CIRP immunogen was compared with other SIIN containing antigens (A) or with untargeted SIIN plus CIRP (B). Immunization was also carried out in IFNAR KO mice (C).

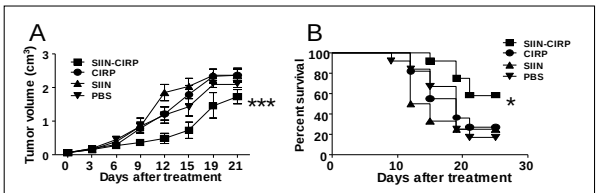

Figure 3. Vaccination with SIIN-CIRP has therapeutic anti-tumor effect. Mice with EG.7-OVA tumors were vaccinated with SIIN-CIRP, SIIN or CIRP and tumor growth (A) and animal survival (B) were monitored.

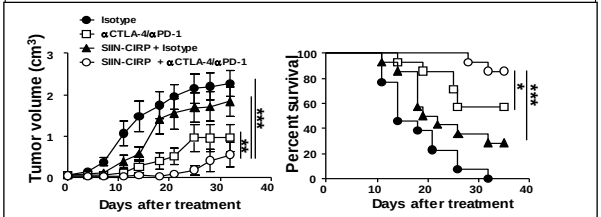

Figure 5. Antitumor therapeutic effect of CIRP vaccine + checkpoint inhibitors. Mice with B16-OVA tumors were vaccinated with SIIN-CIRP, with or without CTLA-4 and PD-1 blockade and tumor growth and animal survival were monitored

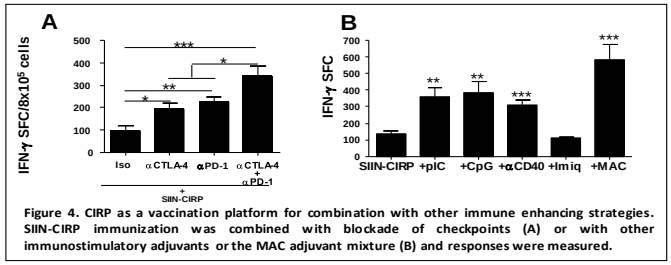

Figure 4. CIRP as a vaccination platform for combination with other immune enhancing strategies. SIIN-CIRP immunization was combined with blockade of checkpoints (A) or with other immunostimulatory adjuvants or the MAC adjuvant mixture (B) and responses were measured.

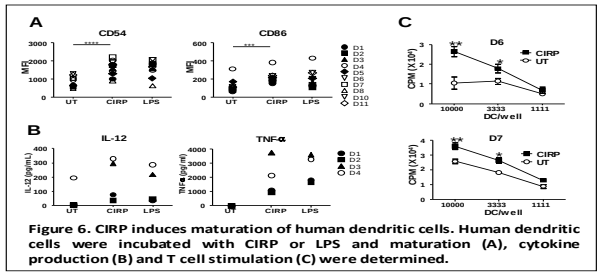

Figure 6. CIRP induces maturation of human dendritic cells. Human dendritic cells were incubated with CIRP or LPS and maturation (A), cytokine production (B) and T cell stimulation (C) were determined.

Intellectual Property European patent application No EP 17382115.8 filed (unpublished)

Contact: Business Development | Email: bdcima@unav.es ; Tel: +34 948 194 700