ImmunoTools *special* Award 2015

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Studies using Chimeric Antigen Receptors for tumor Immunotherapy

Tumor infiltrating T cell lymphocytes harbour a huge potential as antitumor agents if they can be properly expanded and further re infused into patients. New data on checkpoint blockade antibodies reinforce this concept showing that unleashing T cell function in vivo can lead to strong antitumor responses leading to cure in a fraction of patients.

In the last years, genetic manipulation of T cells has been exploited in order to redirect T lymphocyte specificity and increase their functions, turning these cells into live therapeutic agents. Recent reports on these strategies have brought T cell based immunotherapy to a leading role in cancer therapies.

Our group has been developing studies on the genetic manipulation of T lymphocytes by promoting the expression of a transgenic molecule named Chimeric Antigen Receptor (CAR). This molecule has been designed to harbour an anti antigen domain (a single chain fragment variable derived from an antibody), a hinge and transmembrane domain and signalling domains in its intra cytoplasmatic portion. This configurations leads to T cell activation upon antigen recognition, promoting target cell lysis and tumor regression in recently reported clinical trials performed by other groups.

Additional genetic manipulations of the CAR bearing T cells can also be performed in order to promote stronger antitumor responses and turn these cells refractory to local immunomodulation by the tumor environment.

The selection of the target antigen is very challenging when redirecting T cells for therapy, and only few antigens have demonstrated safe as immunotherapy targets so far. In this context, introducing in the T lymphocytes CAR systems that will base the T cell activation on combinations of target antigen recognitions instead of recognizing single target antigens can lead to a safer pattern of T cell responses in vivo, increasing the number of tumors that can be approached using this strategy.

Our group has been developing such combination systems by co-expressing CARs bearing partial T cell activation domains (such as the zeta chain and co-stimulation molecule domains) or activating CARs in combination with CARs bearing inhibitory receptors signalling domains. Such strategies showed to enable T cells to selectively respond to the combination of targets, increased the selectively of the response in reports published by other groups. In addition to the work on the increased selectivity of T cell responses based on CAR combinations, we are working on additional manipulations on the T cells to increase their potential to respond to tumors. One of such approaches is co-expressing CARs and microRNAs predicted to increase T cell responses. We have developed a transgene cassette to concomitantly co-express CARs and microRNAs and are currently evaluating the impact of these combinations on the increase of the antitumor response obtained by expressing only the CAR on T cells.

ImmunoTools reagents will be important to determine the modifications in T cell expression molecule patterns, cytokine production and target cell lysis, unveiling the real impact of the transgene based therapies being tested.

ImmunoTools *special* AWARD for **Martin Hernan Bonamino**
includes 25 reagents

FITC - conjugated anti-human CD3, CD19, CD56, Control-IgG1, Annexin V

PE - conjugated anti-human CD3, CD4, CD27, CD62L, Control-IgG1, Annexin V

APC - conjugated anti-human CD4, CD8, CD44, Control-IgG1, Annexin V

human ELISA-set for 96 wells, rh IFNy, rh TNFa, rh IL-10 (each 3 reagents)

recombinant human cytokines: rh Flt3L, rh FGF-b DETAILS more AWARDS