Cancer immunotherapy can be viewed as “The Breakthrough of 2013”, switching cancer treatment from targeting the tumor to targeting the immune system.

The blockade of immune checkpoints with antibodies (Ab) anti-CTLA-4, anti-PD1 and anti-PD-L1, has given impressive clinical results and manageable safety profiles. As reports of therapeutic efficacy with checkpoint inhibitors extend from metastatic melanoma, renal cell carcinoma and lung cancer to other tumors, the opportunity arises for other type of cancer patients, including breast, ovarian, head & neck (H&N), and paediatric tumours to benefit from these new therapies. There is no doubt that in the upcoming years, immunotherapy will represent a substantial part of the therapeutic arsenal to treat cancer.

3- Our main research programs and achievements:

a. Immunotherapy studies based on the analysis of human tumor-draining lymph nodes (LNs).

We are performing a holistic comparison of the immune profile of invaded versus non-invaded LNs. Our aim is to identify immunomodulatory mechanisms associated to the presence of the invading tumor in the LNs, and to discover biomarkers that could guide the design of patient-tailored immune therapies. Techniques: phenotypic and functional analysis of tumor, fibroblasts, B and T, DCs and NK cells by multi-parametric flow cytometry, ELISPOT, LUMINEX, RNAseq, phage display…. We have established national and international collaborations with groups expert in each of the subpopulation studied. We have created a lymph node collection for research purposes. One special focus is the study of tumor neoepitopes for future personalized anti-cancer vaccines.
b. Translation of IL-2/anti-IL-2 Ab complexes immunotherapy to the clinics

The FDA has already approved high-dose IL-2 therapy for metastatic melanoma and renal carcinoma treatment. However, high-dose of IL-2 administration is highly toxic and has low efficacy. In this project, we want to use IL-2/anti-IL-2 complexes directed to CD8+ and NK T cells, in view of clinical application, as monotherapy or combined with other immunotherapies in different tumor mouse models.

c. Study immunotherapies in optimized in vivo models for cancer

To improve our understanding and to build better and more translatable in vivo mouse tumor models, we are developing humanized mouse models consisting of the transplant of patient-derived tumor xenografts into immunodeficient mice reconstituted with human immune cells (isolated from the matching patient from the draining LNs or with allogenic PBMCs or LN cells). This is a collaborative project with the Laboratory of Preclinical Investigation, LIP. The final aim is improving therapeutic effect and defining rationalized drug combinations with immune checkpoints and proprietary molecules developed by collaborators, including novel immunomodulatory approaches generated at our unit. Also, using this model we are evaluating the role of microbiota on the response to anti-PD-1 Ab treatment.
Key publications

**Year of publication 2017**

Fernando P Canale, Maria C Ramello, Nicolas Núñez, Cintia L Araujo Furlan, Sabrina N Bossio, Melisa Gorosito Serrán, Jimena Tosello Boari, Andrés Del Castillo, Marta Ledesma, Christine Sedlik, Eliane Piaggio, Adriana Gruppi, Eva V Acosta Rodríguez, Carolina L Montes (2017 Oct 26) **CD39 expression defines cell exhaustion in tumor-infiltrating CD8+ T cells.**
*Cancer research* : DOI: canres.2684.2016

Rodrigo N Ramos, Eliane Piaggio, Emanuela Romano (2017 Mar 19) **Mechanisms of Resistance to Immune Checkpoint Antibodies.**
*Handbook of experimental pharmacology* : DOI: 10.1007/164_2017_11

**Year of publication 2016**
Nature communications : 13027 : DOI : 10.1038/ncomms13027

Oncoimmunology : e1171434 : DOI : 10.1080/2162402X.2016.1171434

Year of publication 2015


Journal of immunology (Baltimore, Md. : 1950) : 2117-27 : DOI : 10.4049/jimmunol.1401551