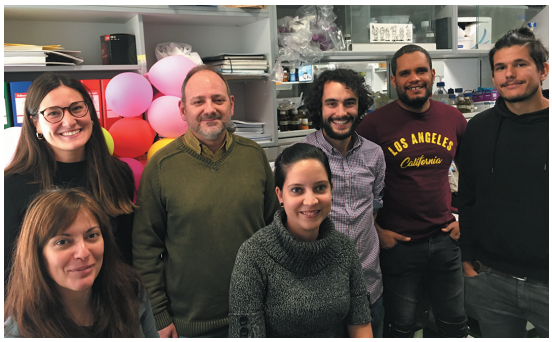
GROUP LEADER
Domingo F. Barber Castaño

SENIOR SCIENTIST
Vladimir Mulens Arias

TECHNICIAN
Sonia Pérez-Yagüe (Lab Manager)

PhD STUDENTS
Neus Daviu Bou
David Egea Benavente
Andrés París Muñoz
Yadileiny Portilla Tundidor
Laura Sanz Ortega

MASTER STUDENTS
Gonzalo Aizpurua de Arteche



Nanomedicine, cancer immunotherapy and autoimmune diseases

Magnetic Iron oxide nanoparticles (MNPs) have considerable potential to be used as nanomedicines for targeted drug release or magnetic resonance imaging. More recently, we highlighted the promise of using MNPs in other therapeutic approaches to treat cancer, such as the induction of intracellular hyperthermia in tumour cells or the magnetic targeting/retention of lymphocytes in cell transfer therapies. We have also seen that the accumulation of MNPs by different cell types induces oxidative stress and its associated effects as a consequence of MNP degradation. Thus, here we aim to explore whether these responses could be used therapeutically to fight tumours at different levels.

The overall objective of our group is to fully understand the molecular and cellular mechanisms induced by MNPs at their different levels of action. This knowledge can be used to improve the functional design of MNPs for specific biomedical applications, such as therapies to combat tumours and autoimmune diseases, with the aim of bringing them closer to their clinical application. As such, we will pursue five specific objectives: 1) We will expand our studies on the magnetic retention/accumulation of MNP-functionalized anti-tumour lymphoid cells in ACT therapies in order to bring this therapy closer to the clinic; 2) We intend to explore whether the targeting to and/or retention of MNP loaded tolDCs in LNs could ameliorate the symptoms of lupus in the MRL/lpr mouse model of SLE; 3) We will evaluate the capacity of the oxidative stress induced in cells by MNPs to remodel the tumour microenvironment and to improve anti-cancer therapies; 4) We will assess how to improve the efficiency of intracellular heating of MNPs in AMF-induced hyperthermia strategies, studying the biological effects induced by MNPs of different physico-chemical characteristics (size, shape, anisotropy) after the application of an AMF of different intensity and frequency; 5) We will analyse whether oxidative and endoplasmic reticulum (ER) stress caused by MNPs inside tumour cells could affect the processing and presentation of antigens, and whether this might provoke the generation of neoantigens.

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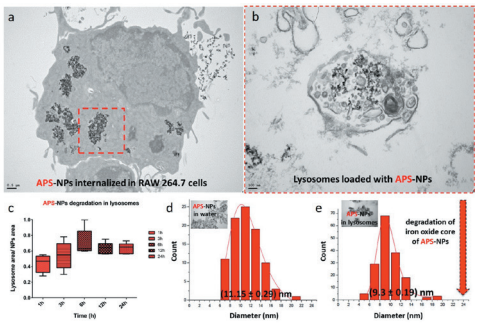

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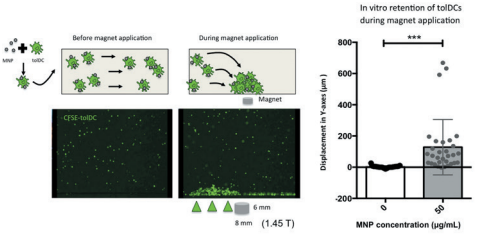

1 ***Lysosomal degradation of superparamagnetic iron oxide nanoparticles inside of macrophages.*** *(a) TEM images of typical subcellular localizations of APS-NPs. RAW 264.7 cells were exposed to 125 µg/mL APS-coated iron oxide nanoparticles in DMEM for 24 hours. After 24 hours most of the observed particles were found inside lysosomes. (b) TEM images of the organellar fractions isolated by magnetic extraction from cells treated for 24 h with APS-NPs confirmed presence of nanoparticles in the isolated organelles. (c) Size reduction of APS-NPs during the degradation process inside the lysosomes over 24h. Transmission electron micrographs of the APS-NPs at the initial (d) and final (e) points of the degradation process together with the particle core size distribution measurements obtained from the TEM images. Scale bar: 100 nm. (Yadileiny Portilla).*

2 *Retention of tolerogenic dendritic cells (tolDCs) associated to Magnetic nanoparticles (MNPs) using a neodymium magnet of 1.45 T (8 x 6 mm) in a*

SELECTED PUBLICATIONS

Sanz-Ortega L, Rojas JM, Portilla Y, Pérez-Yagüe S, Barber DF. Magnetic nanoparticles attached to the NK cell surface for tumor targeting in adoptive transfer therapies does not affect cellular effector functions. Front Immunol 2019; 10: 2073.

Mulens-Arias V, Rojas JM, Sanz-Ortega L, Portilla Y, Pérez-Yagüe S, Barber DF. Polyethylenimine-coated superparamagnetic iron oxide nanoparticles impair *in vitro* and *in vivo* angiogenesis. Nanomedicine 2019; 21: 102063.

Sanz-Ortega L, Portilla Y, Pérez-Yagüe S, Barber DF. Magnetic targeting of adoptively transferred tumour-specific nanoparticle-loaded CD8+ T cells does not improve their tumour infiltration in a mouse model of cancer but promotes the retention of these cells in tumour-draining lymph nodes. J Nanobiotechnology 2019; 17(1): 87.

Del Sol-Fernández S, Portilla-Tundidor Y, Gutiérrez L, Odio OF, Reguera E *et al.* Flower-like Mn-Doped magnetic nanoparticles functionalized with αvβ3-integrin-ligand to efficiently induce intracellular heat after alternating magnetic field exposition, triggering glioma cell death. ACS Appl Mater Interfaces 2019; 11 (30): 26648-26663.

Sanz-Ortega L, Rojas JM, Marcos A, Portilla Y, Stein JV, Barber DF. T cells loaded with magnetic nanoparticles are retained in peripheral lymph nodes by the application of a magnetic field. J Nanobiotechnology 2019; 17 (1): 14.