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WHAT IS NEW? WHAT IS HOT?

Nanotherapy that prevents trained immunity and promotes tolerance

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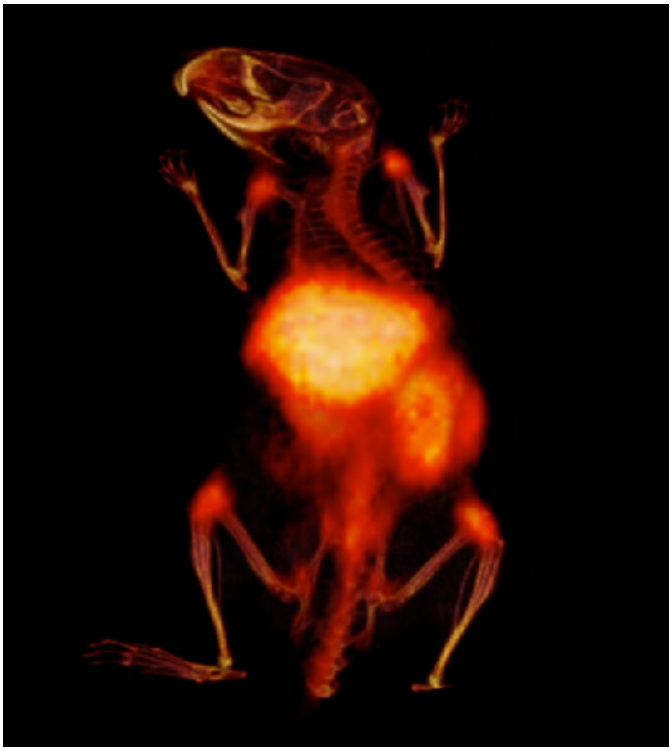
Investigators at the Icahn School of Medicine at Mount Sinai in New York, USA reported a novel nanoimmunotherapy that targets myeloid cells *in vivo* in the November 2018 issue of the journal *Immunity*. Senior authors Drs. Jordi Ochando and Willem Mulder spearheaded an extensive effort in which this nanoimmunotherapy was applied to an experimental mouse model of organ transplantation. Using a short-term regimen, long-term acceptance of the transplanted organ was achieved in the absence of serious side effects.[1]

The nanomimmunotherapy consisted of high-density lipoprotein (HDL) nanobiologics, which they previously reported to specifically target myeloid cells *in vivo*.[2] In the current study, the authors demonstrate that HDL-nanobiologics target myeloid cells in the heart allograft and myeloid cell precursors in the bone marrow of transplant recipient mice. The latter characteristic of HDL-nanobiologics is critical for the long-term efficacy. The authors hypothesize that myeloid precursors in the bone marrow, such as MDP and CDP, are deactivated before they are mobilized into circulation (Fig. 1).

To prevent myeloid cells' activation after transplantation, an inhibitor of the mammalian target of rapamycin (mTORi) was incorporated into HDL-nanobiologics. The resulting mTORi-HDL nanobiologics were tested for their ability to prevent inflammatory cytokine production of human monocytes, which were activated *in vitro* with β-glucan and lipopolysaccharide (LPS). The data demonstrate that

Fig 1: Positron Emission Tomography/Computed Tomography 3D image shows that HDL nanobiologics labeled with Zirconium-89 (89Zr) accumulate in the bone marrow, which is critical for long-term therapeutic effects of HDL nanobiologics



mTORi-HDL nanobiologics prevented epigenetic rewiring and glycolytic metabolism activation of human monocytes associated with trained immunity.

Trained immunity is a recently discovered functional state of myeloid cells, which is characterized by non-permanent epigenetic and metabolic underlying potent pro-inflammatory responses.[3] Drs. Mulder and Ochando demonstrate that the transplanted allograft induces training of graft-infiltrating macrophages. A short-term mTORi-HDL nanoimmunotherapy during the first week after transplantation prevented the development of trained macrophages in the allograft. Remarkably, mTORi-HDL nanobiologics induced the accumulation of regulatory macrophages that prevented CD8+ T cell proliferation and promoted CD4 Treg cell expansion. To enhance therapeutic efficacy, the authors complemented the mTORi-HDL treatment with a CD40-TRAF6 specific nanobiologic (TRAF6i-HDL) that inhibits co-stimulation.[2] This synergistic nanoimunnotherapy resulted in indefinite allograft survival, without signs of toxicity.

This innovative strategy, focused on preventing trained immunity, is a major advancement in the field and represents a potential clinical treatment for transplant patients. Since there are no clinical treatments that specifically target myeloid cells *in vivo*, HDL-based nanobiologics that prevent inflammatory innate immune responses provides a framework for developing novel therapies to promote immunological tolerance in other clinical scenarios such as autoimmunity, chronic inflammatory diseases and allergies.

Competing interests

The authors declare that they have no competing interests.

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