Listeria based nanovaccines as immunotherapies for solid tumours

Valdecilla Instituto de Investigación Sanitaria IDIVAL

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1. The institution

Valdecilla Biomedical Research Institute (IDIVAL)

- **Founded by the government of Cantabria and the University of Cantabria (UC).**
- **IDIVAL promotes and develops research and innovation in the biomedical environment of Cantabria whose epicentre is the Valdecilla Universitary Hospital (HUMV).**
- **Since 2015, IDIVAL is accredited by the Spanish Institute of Health Carlos III as one of the reference Institutes for Health Research in our country.**
- **In 2017, Impact Factor: 2047; Budget: €6.94M**

1. The Research Group

- **Principal Investigator:** *Dra. Carmen Alvarez Dominguez* (PhD Immunology)

- **Project group: three Oncologists** (*Dr. Fernando Rivera* MD, PhD Medicine, *Dra. Almudena Garcia*, MD & *Dr. Ignacio Durán*, MD, PhD Medicine, HUMV), **a Dermatologist** (*Dra. Sonsoles Yañez Diaz,* MD, PhD Medicine, HUMV), **two Anatomopathologists** (*Dr. Javier Gomez-Roman* MD, PhD Medicine & *Dr. Javier Freire*, PhD Molecular Biology, HUMV), **two post-doctoral fellows** (*Dr. Ricardo Calderon-Gonzalez & Dra. Elisabet Frande*, PhD Biomedicine, IDIVAL), **two pre-doctoral students** (*Dº Hector Terán-Navarro*, Chemist-MS Nanomedicine & *Dº David Salcines-Cuevas*, Biotechnologist, IDIVAL), **an Innovation Engineer** (*Dª Patricia Zorilla*, MS Telecommunications, IDIVAL).

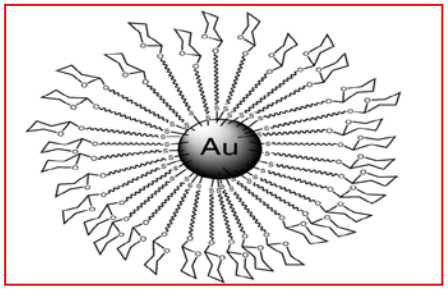
- **Two research lines:**
  - Design *Listeria* based nanovaccines as immunotherapies for solid tumors
  - Prepare *Listeria* based nanovaccines for prevention of infectious diseases: listeriosis, tuberculosis and pneumonia

- **Funding:** ISCIII (DTS18-00022), INNVAL17/01, LPLV-CI-18-09 & BDP77.

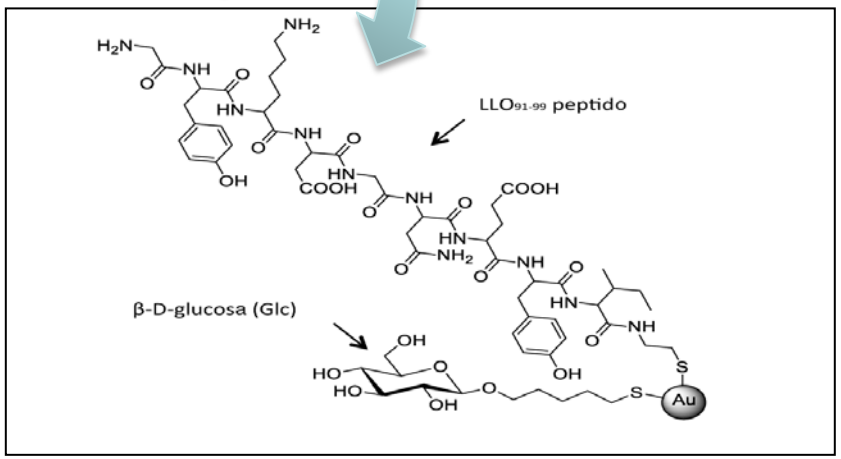
2. The product

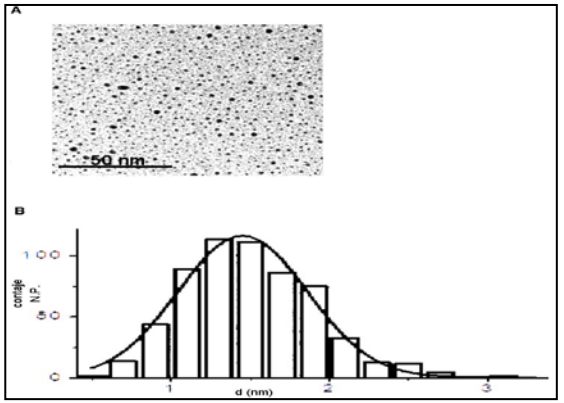
- **Listeria based nanovaccines as immunotherapies for solid tumors.**

❑ Technological origin



AuGNP (GNP)
(gold-glyconanoparticules)





~ 2 nm

- Chemical synthesis and homogeneous size distribution of GNPs

2. The product

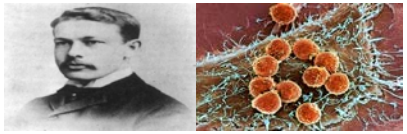
Nanomaterials. 2016; 6, 521
Oncotarget 2016; 7,16855
Oncotarget 2017; 8(33), 53916

- **Listeria based nanovaccines as immunotherapies for solid tumors.**

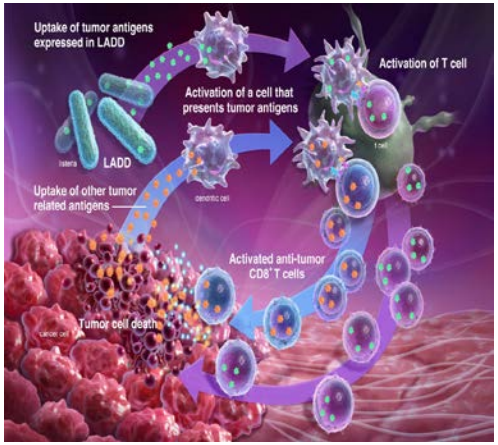
❑ Scientific origin → Cancer Immunotherapy

✓ **Coley toxins → mix streptolysin O/Serratia hemolysin** → tumour treatment

✓ **Listeria attenuated mutants$^{\Delta LLO}$** → vaccine for tumors
(ADX11-01 → severe listeriosis)



1890-1936, W. Coley (surgeon in NY Hospital)



Listeria immunity related to tumors:

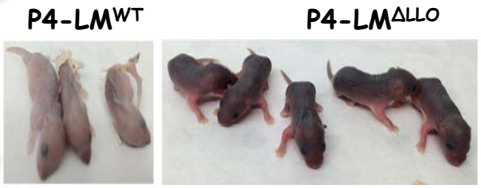
- infiltrates tumor/hypoxia
- induces $CD8^+$ cytotoxic responses
- promotes Th1 cytokine pattern

Cutaneous listeriosis:

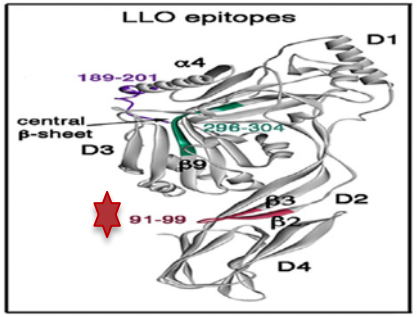
- Skin injuries
- Target to melanocytes
- apoptosis

granulomatosis infantisepticum

$LM^{\Delta LLO}$ →



LLO map into DC vaccines
(LLO$^{91-99}$ anti-tumor epitope)



2. The product

a) Target Indications

a1).- Therapeutic areas

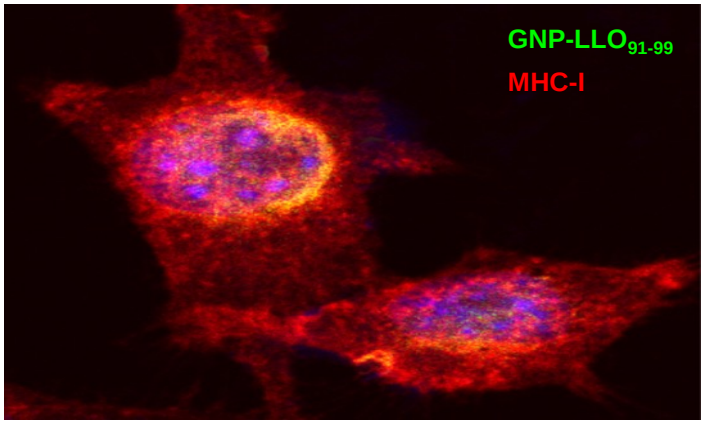
Oncology
Oncoimmunology
Dermatology

Adjuvant

Anti-neoplastic product

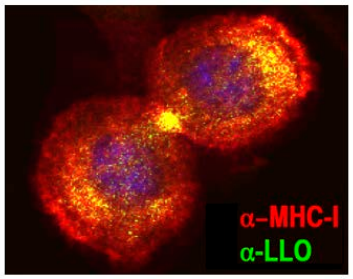
a2).- Target cells

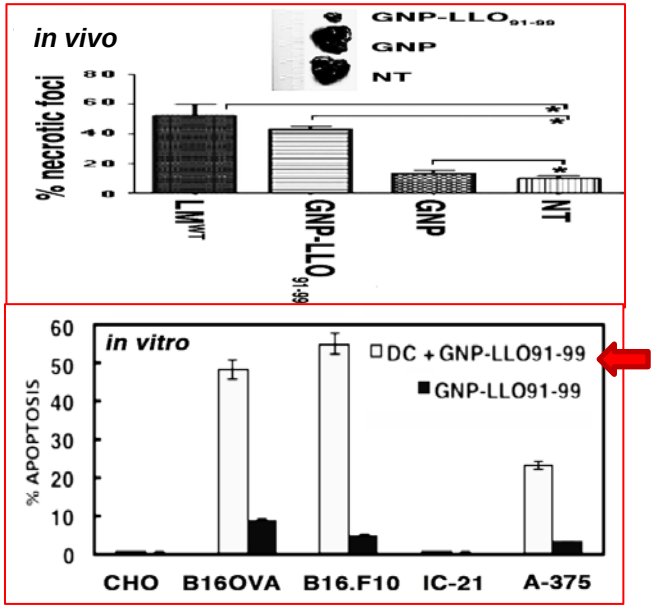
Dendritic cells (Adjuvant)



Tumour cells (immunogenic cell death)

B16.F10+GNP-LLO$_{91-99}$

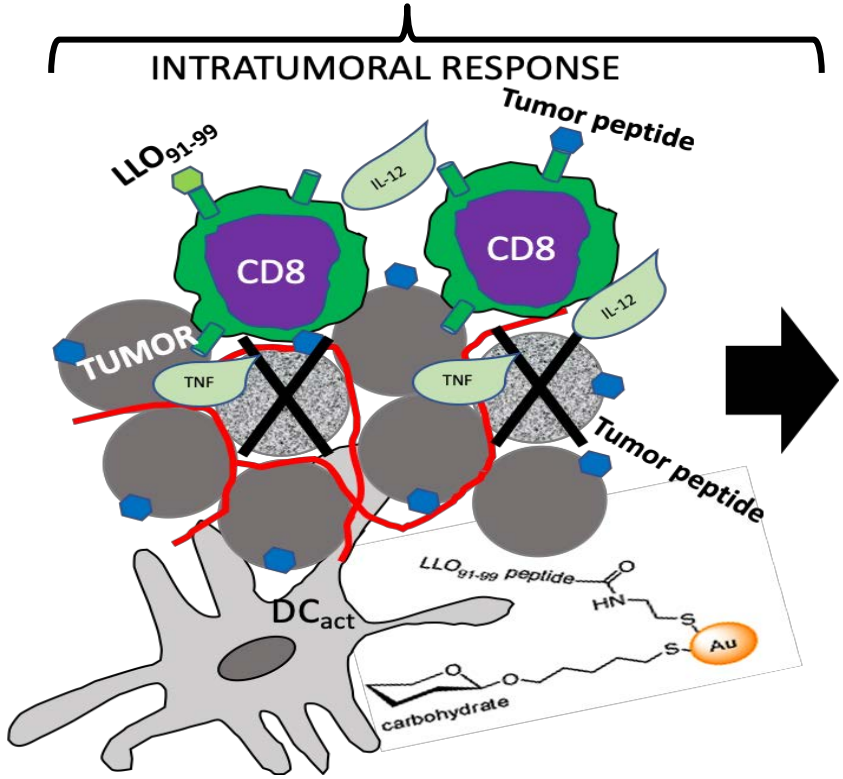




Nanoscale 2017; 9(30), 10721
Patent: P201600160
Oncoimmunology 2018 (in press)

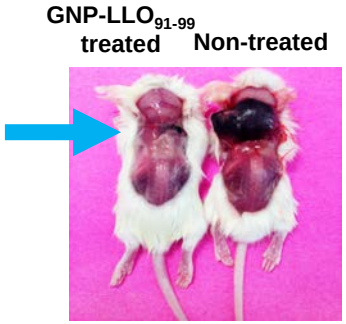
2. The product

b) Innovative mechanism of action

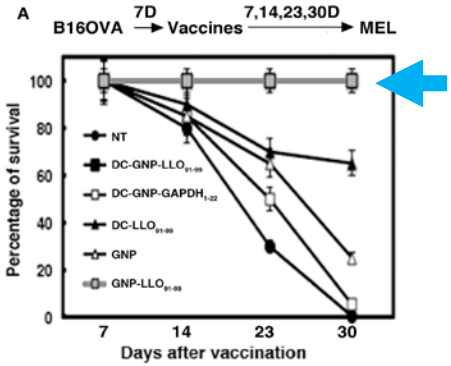


1.- activation of intratumor DC → induce immunogenic tumor cell death (Th1)
2.- expands cytotoxic anti-melanoma T cells

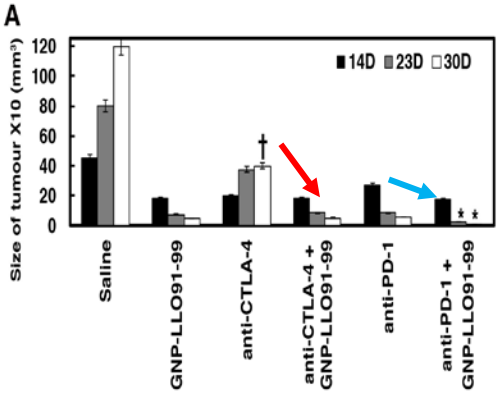
- **Tumor regression**

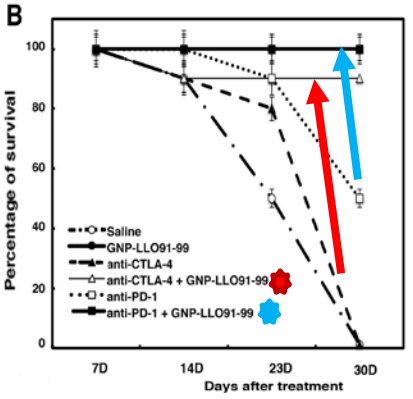


- **Increase overall survival**



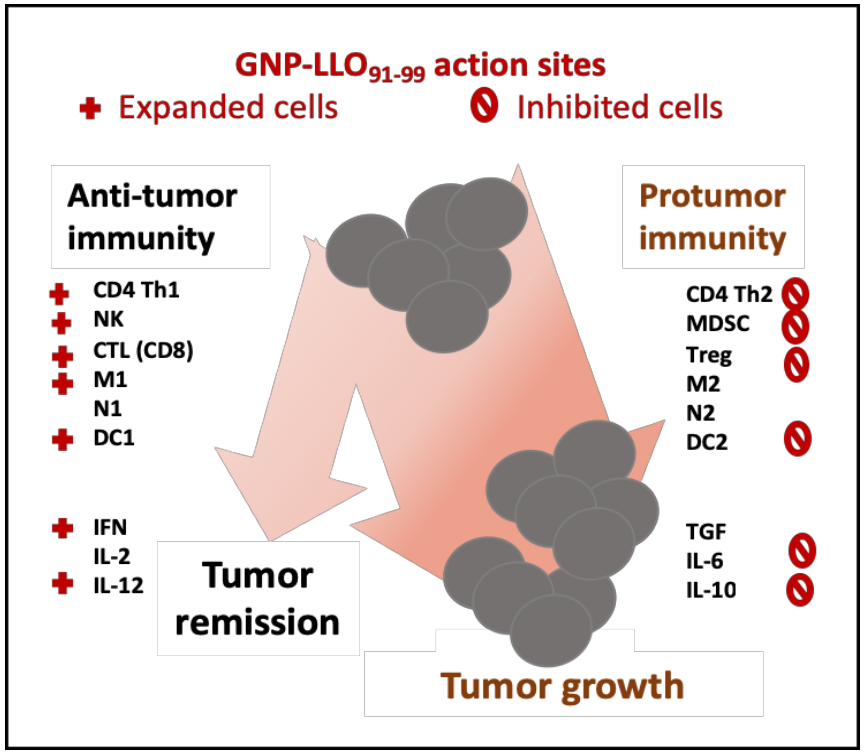
- **Combine well & potentiate checkpoint immunotherapies**





2. The product

c) Differential features facing the market



Nanovaccines target and activate DC to produce Th1 responses (adjuvant effect)

Nanovaccines induce immunogenic melanoma cell death and tumour regression (anti-neoplastic effect: immunotherapy)

- Activated DC expand cytotoxic anti-melanoma T cells
- Activated DC block T_{reg} cells that stops immune responses

- **Breaks the immune balance towards anti-tumor immunity → remission**
- **Enhances overall & disease-free survival**
- **Combines with immunotherapies**

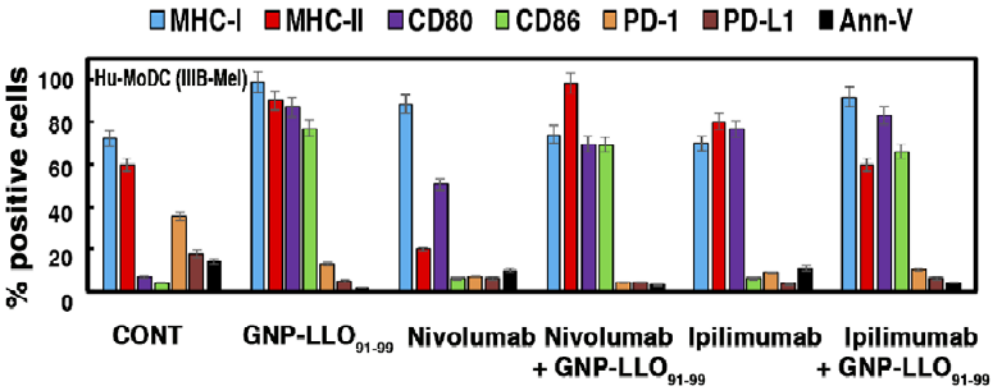
2. The product

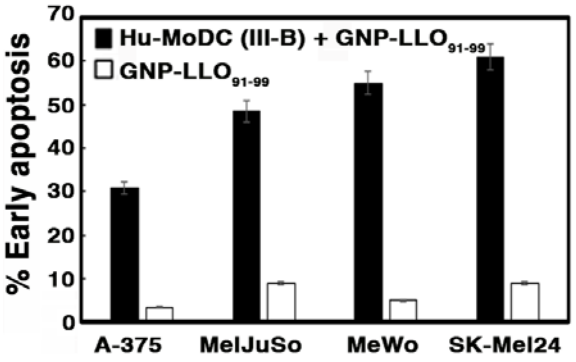
d) Current status of development

1.- Experiments in mice-normal mice- (proof of concept)

2.- Experiments in blood cells of patients-MoDC (pre-clinical studies)

- Human MoDC of a patient with melanoma stage IIIB (resected, IFN-α 2001, heatlhy)





- Monotherapy or in combination with anti-CTLA-4/anti-PD-1 increases expression of activating markers
- $GNP\text{-}LLO_{91\text{-}99}$ induces melanoma apoptosis after incubation with MoDC

3.- Experiments in mice with NSCLC (lung) and glioblastoma: <u>successful</u>

2. The product

e) IPR protection

- A Spanish patent application was filed on 24th February 2016 (ES filing number 201600160).
- On 23rd February 2017 an International patent application was filled (PCT/ES2017/070103) claiming priority of the Spanish patent application. The EPO acts as ISA (International Search Authority).
- After IPER (International Preliminary Examination Report), all the claims are considered to fulfil the requirements of novelty and inventive step.
- The application is currently granted in Spain and under examination at the EPO and USPTO.

2. The product

f) Pitfalls & Risks to be considered

1.- Missing the kinetics of toxicity *in vivo* (mice)

2.- Missing *in vitro* effects of nanovaccines with human MoDC and cytolytic activity against allogenic human melanoma (solid tumors) **other tumors (**NSCLC, CCR, glioblastoma, mama, pancreas….)

3.- Missing *in vivo* experiments with immunodeficient mice (SCID, others….)

3. Partnering opportunities

We need a *partner* that invest in the product development to perform a <u>Phase I clinical assay.</u>

4. Questions

Funding requirement to finish Pre-clinical studies ? 500.000 €

Monetary needs for Phase I clinical assay ? ~ 1.000.000 €