Multivalent vaccines based in gold nanoparticles coupled to peptides: tuberculosis, listeriosis & pneumonia

Madrid, 29 de octubre de 2019

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XVII Encuentro de Cooperación Farma-Biotech

GOBIERNO DE ESPAÑA · MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

Valdecilla Instituto de Investigación Sanitaria IDIVAL

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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 2018, Impact Factor: 2250; Budget: €7.5M

1. The Research Group

- **Principal Investigator:** *Dra. Carmen Alvarez Dominguez* (PhD Immunology)
- **Project group: a Microbiologist** (*Dr. Concepción Perez Del Molino,* MD, PhD Medicine, HUMV), **a Dermatologist** (*Dra. Sonsoles Yañez Diaz,* MD, PhD Medicine, HUMV), **two Anatomo-pathologists** (*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:**
  - **Prepare *Listeria* based nanovaccines for prevention of infectious diseases: listeriosis, tuberculosis and pneumonia**
  - Design *Listeria* based nanovaccines as immunotherapies for solid tumors
- **Funding:** ISCIII (DTS18-00022), INNVAL17/01, TRANSVAL18/03, CI19/16.

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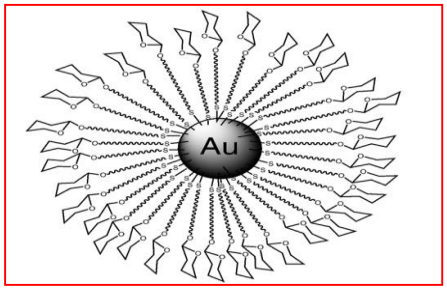
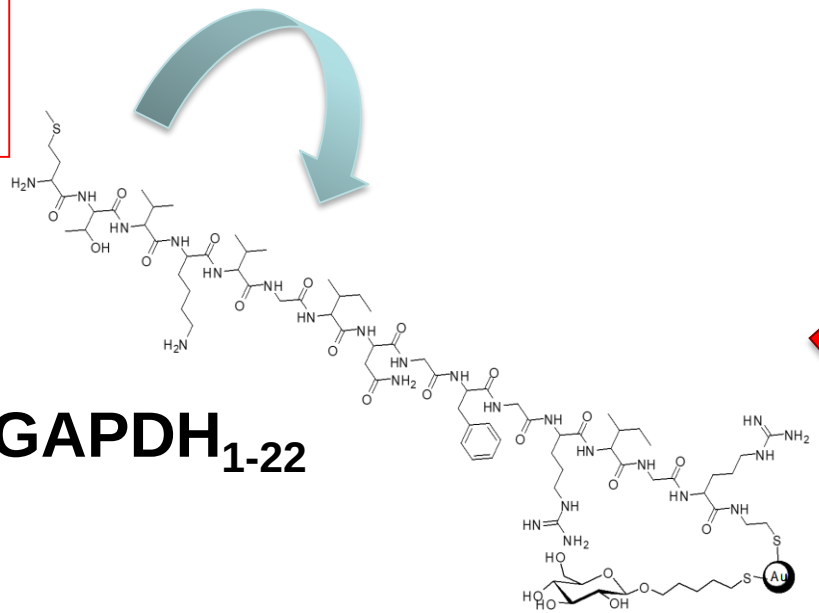
2. The product

- **Multivalent vaccines based in gold nanoparticles coupled to peptides: tuberculosis, listeriosis & pneumonia.**

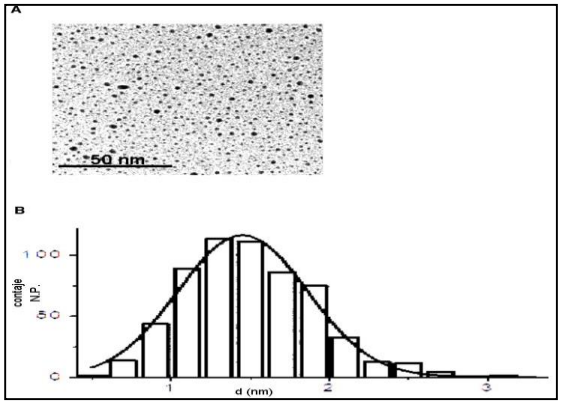
❑ Technological origin



AuGNP (GNP)
(gold-glyconanoparticules)



$GAPDH_{1-22}$

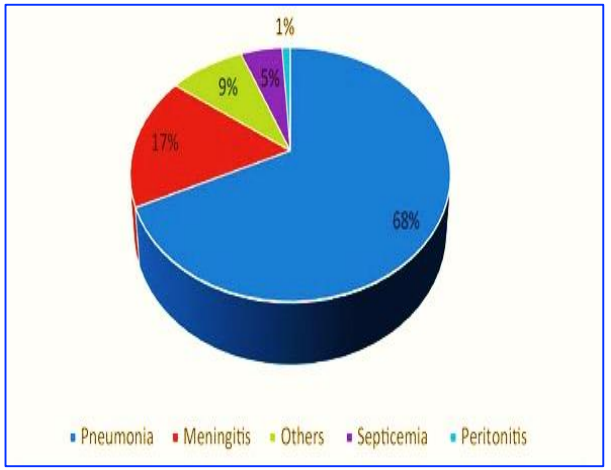


~ 2 nm

- Chemical synthesis and homogeneous size distribution of GNPs

2. The product

- **Multivalent vaccines based in gold nanoparticles coupled to peptides: tuberculosis, listeriosis & pneumonia.**

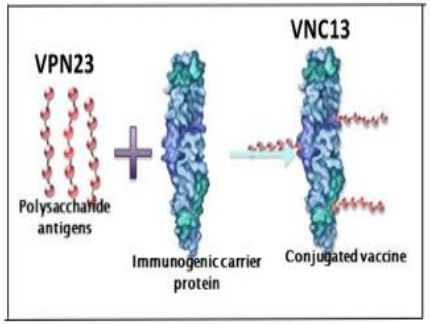


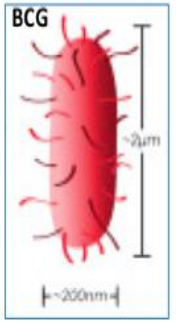
❑ Scientific origin → Prevention against infections

✓ **Main clinical syndromes affecting adults (bacteria)**
- ❑ 68% pneumonia → 17% meningitis → 5% septicemia

✓ **Severe bacterial infectious diseases in adults: pneumonia, meningitis, lung tuberculosis, listeriosis**
→ elderly, immunocompromised patients

✓ **Current challenge in vaccination of adults:**
- ❑ Immune senescence (basal state of inflammation)
- ❑ Available commercial vaccines → low effect in adults
  - ➢ **VPN23/VNC13** (pneumonia), **BCG** (tuberculosis)
  - ➢ **No one available** (listeriosis)





1. **Need of vaccines for *Streptococcus, Mycobacterium, Listeria***
2. **Common population at high risk → justify multivalent vaccines**
3. **Search for an antigen →to include in multivalent vaccine designs**

2. The product

a) Target Indications

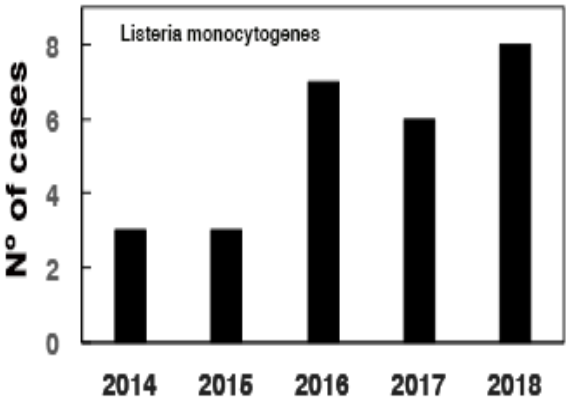
a1).- Therapeutic areas

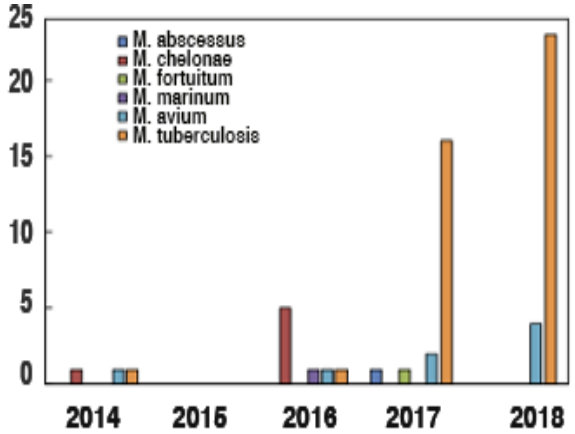
- Infectious Diseases (Microbiology)
- Oncology /Reumatology
- Immunology/Vaccinology

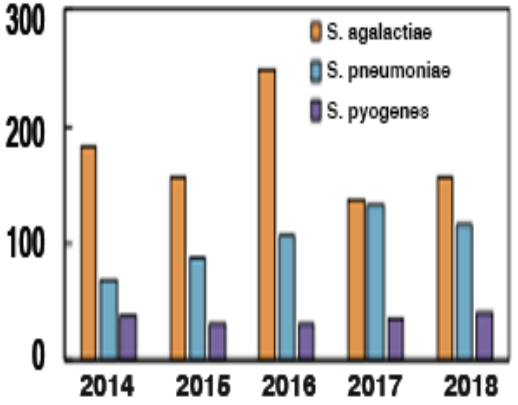
a2).- Target population

→ individuals older than 50 years

Retrospective 5-years study on older than 50 years in HUMV:







- *M. tuberculosis* (2-23 cases)
- *L. monocytogenes* (3-8 cases)

- *S. pneumoniae* (68-132 cases)
- *S. agalactiae* (156-248 cases)
- *S. pyogenes* (31-41 cases)

- **4-10 fold more re-emergent meningitis-respiratory bacteria → tuberculosis/meningitis**
- **High & stable numbers of pneumonia-meningitis bacteria → pneumonia/meningitis/ severe cutaneous forms**

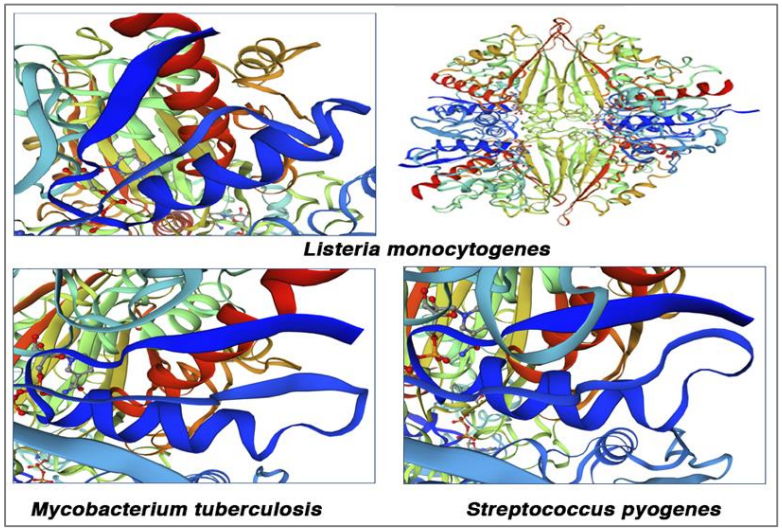
2. The product

a) Target Indications

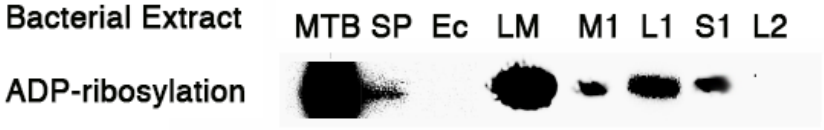
a3).- Target antigen → glyceraldehyde-3-phosphate dehydrogenase (GAPDH)

	15-aa	Sequence homology
L. monocytogenes	MTVKVGINGF GRIGRLAFRR IKEVSDDIEV....	
M. tuberculosis	MTVRVGINGF GRIGRNFYRA LLAQQEQGTA....	95%
M. avium	MTVRVGINGF GRIGRNFYRA LLAQQEQGTA....	95%
M. leprae	MTVRVGINGF GRIGRNFYRA LLAQQEHGIA....	95%
M. marinum	MTVRVGINGF GRIGRNFYRA LLAQQEQGTA....	95%
S. pneumoniae	MVVKVGINGF GRIGRLAFRR IQNIEGVEVT....	95%
S. pyogenes	MVVKVGINGF GRIGRLAFRR IQNIEGVEVT....	95%
S. aureus	MAVKVAINGF GRIGRLAFRR IQEVEGLEVV....	90%
P. aeruginosa	MTIRLAINGF GRIGRNVLRA LYTGHYREQL....	60%
Homo sapiens	MGKVKVGVNG FGRIGRLVTR AAFNSGKVDI....	45%
Mus musculus	MVKVGVNGFG RIGRLVTRAA ICSGKVEIVA....	42%

$GAPDH_{1-22}$ peptide: common 3D structure



→ Common ADP-ribosylation activity on Rab5a



→ $GAPDH_{1-15}$ peptide: minimal unit of effect

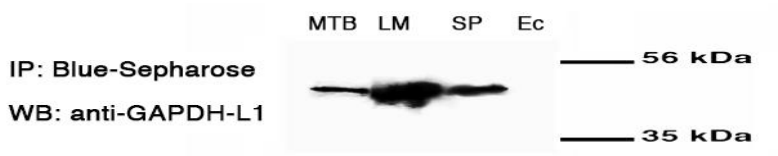
2. The product

a) Target Indications

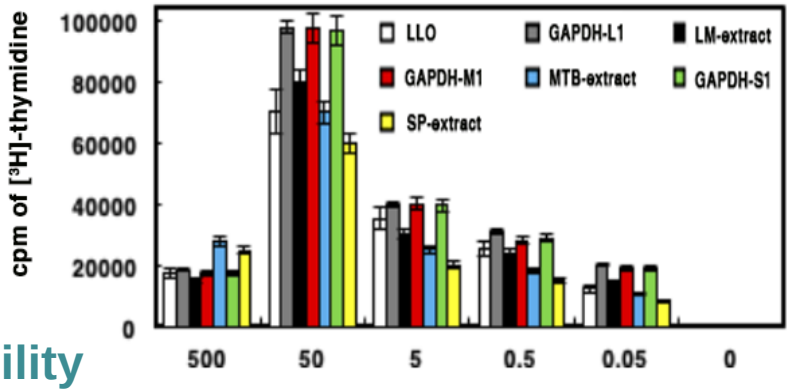
a4).- Target epitope → glyceraldehyde-3-phosphate dehydrogenase (GAPDH)

GAPDH1$_{-22}$ peptide → Common immunogenic capacity

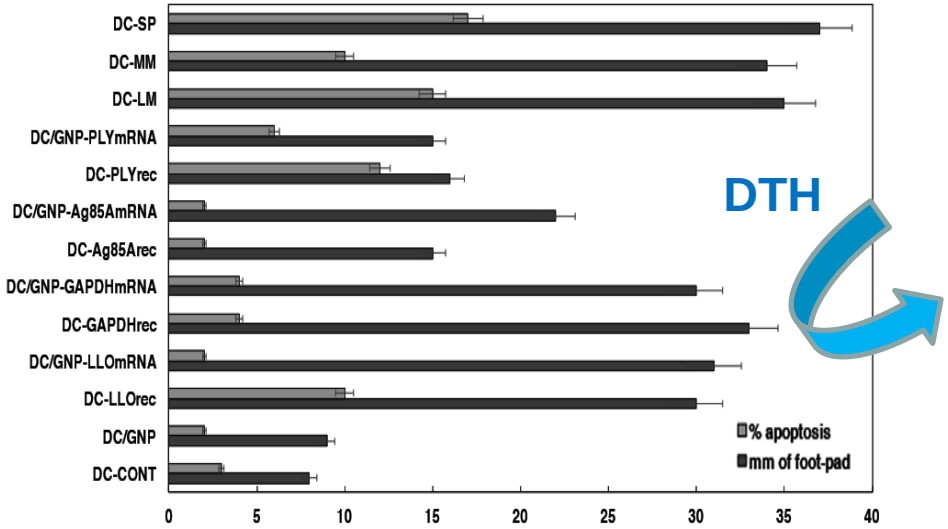
Antibody recognition



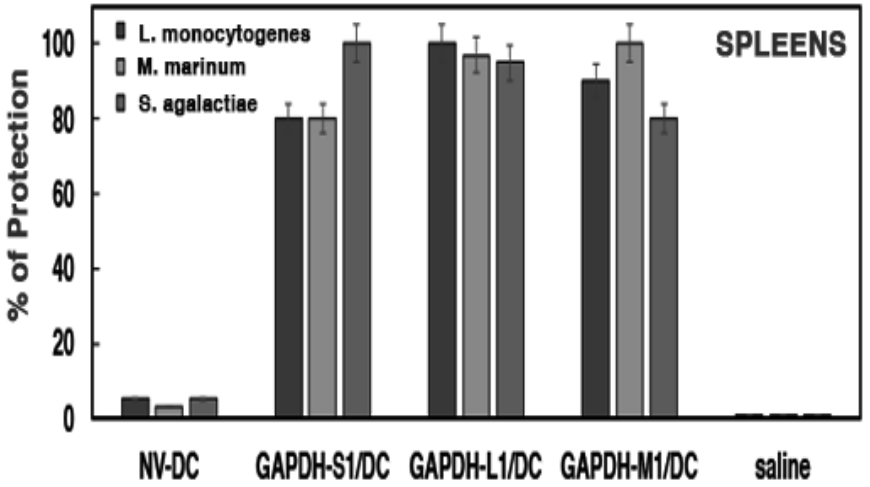
DTH response/foot pads



GAPDH1$_{-22}$ peptide → Common protection ability



DTH

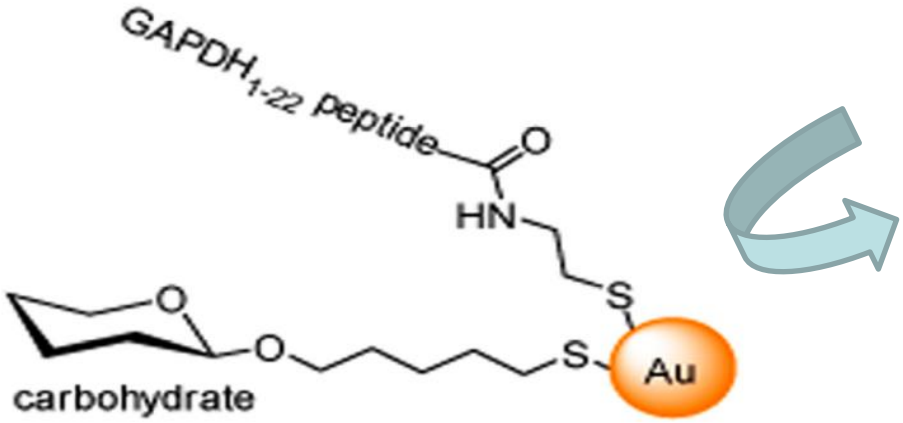


2. The product

Patent: ES201830628.
Application date: 28/02/2018.
PCT/ES2019/070413

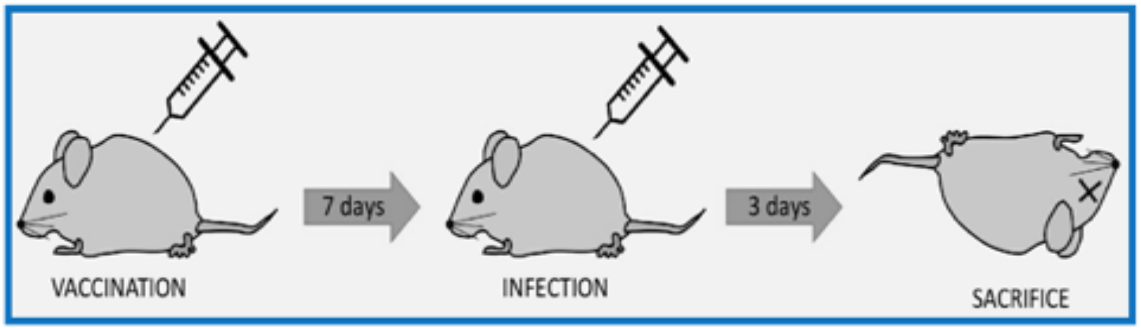
a) Target Indications

a5).- Vaccine design → GNP-GAPDH$_{1-22}$/GNP-GAPDH$_{1-15}$ + adjuvant



GAPDH$_{1-15}$

L. monocytogenes	MTVKVGINGF GRIGR
M. tuberculosis	MTVRVGINGF GRIGR
M. avium	MTVRVGINGF GRIGR
M. leprae	MTVRVGINGF GRIGR
M. marinum	MTVRVGINGF GRIGR
S. pneumoniae	MVVKVGINGF GRIGR
S. pyogenes	MVVKVGINGF GRIGR



Vac sites: ***ip***
iv
sc

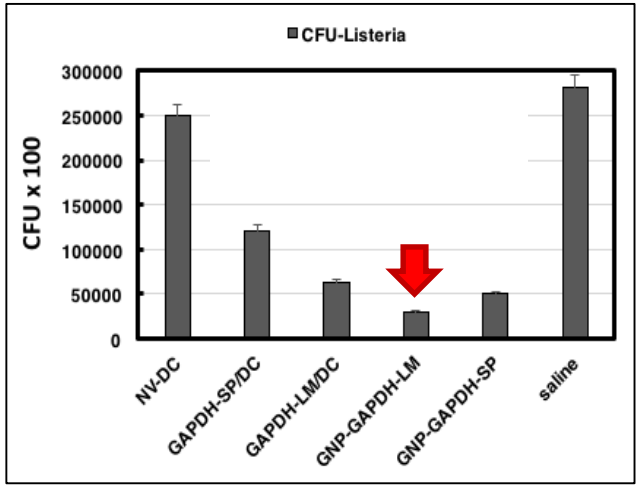
ADVAX TLR2 **DIO-1** TLR2/TLR4 → **adjuvants**

2. The product

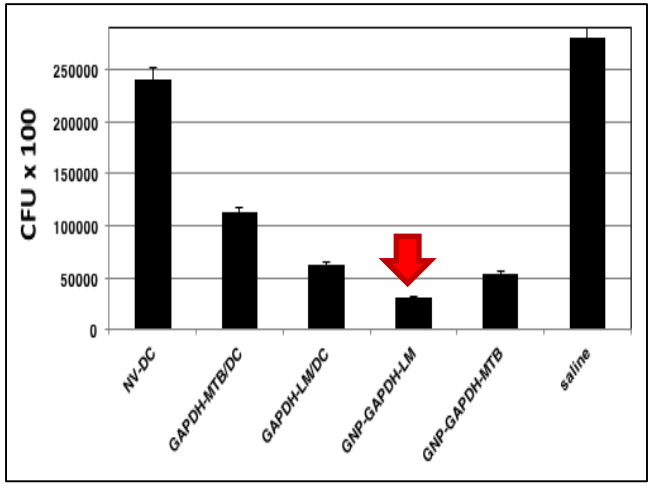
b) Innovative mechanism of action of $GAPDH_{1-22}$ peptide

- **$GAPDH_{1-22}$/DC vaccine → show multivalent ability**
- **GNP-$GAPDH_{1-22}$ + DIO-1 → multivalent capacity higher than DC (vac site + infection: iv)**
  - Protection in listeriosis mice models
  - Protection in lung and cutaneous tuberculosis mice models
  - Protection in pneumonia mice models

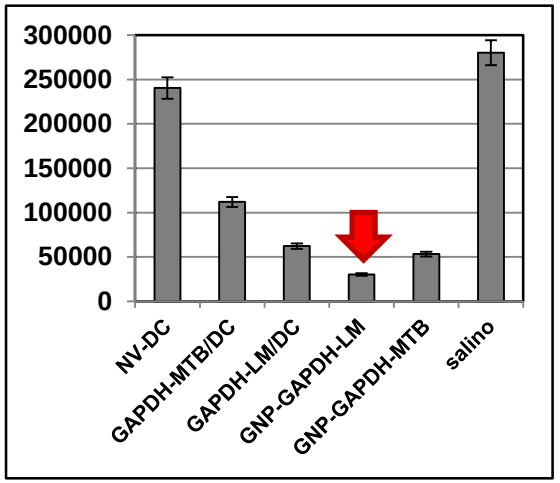
Protection in listeriosis



Protection in cutaneous tuberculosis (*M. marinum*)



Protection in pulmonar tuberculosis (*M. smegmatis*)

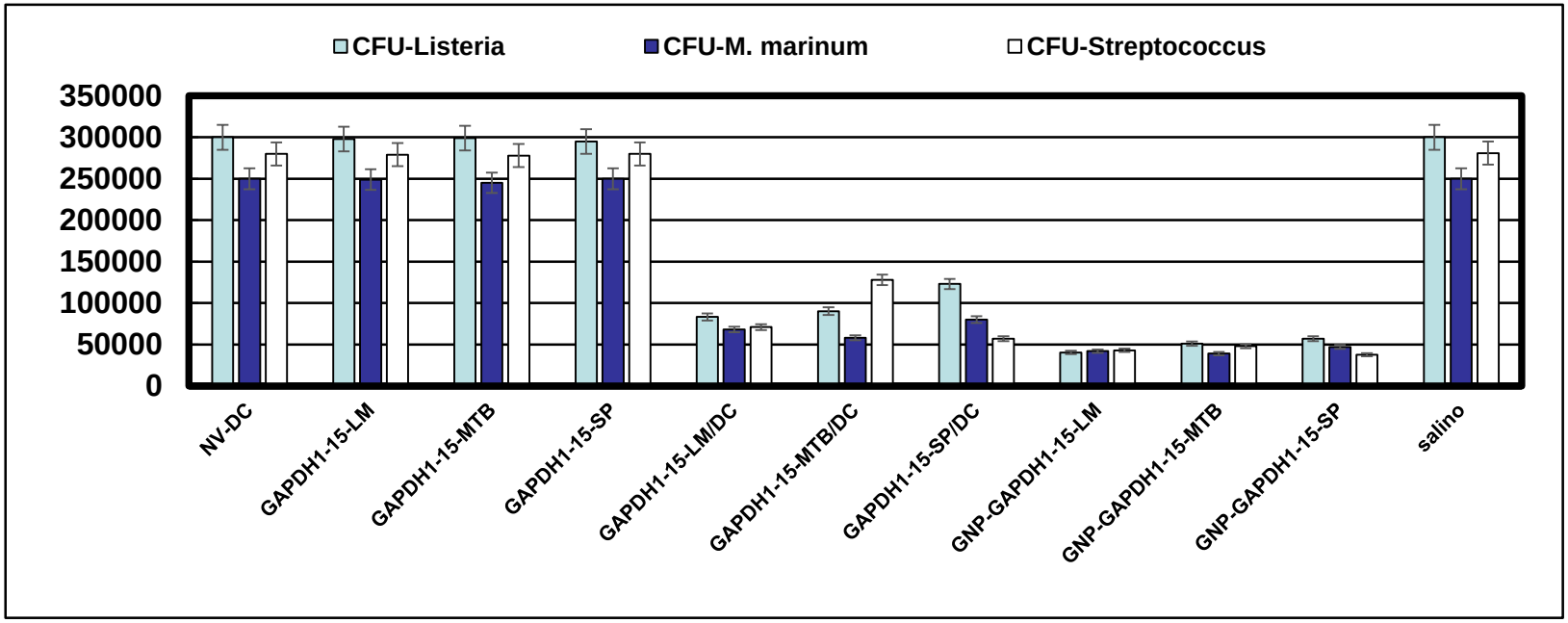


- GNP-$GAPDH_{1-22}$-LM vaccine showed the highest protection ability

2. The product

b) Innovative mechanism of action of $GAPDH_{1-15}$ minimal peptide

- **$GAPDH_{1-15}$/DC vaccine → minimal epitope with multivalent ability**
- **GNP-$GAPDH_{1-15}$ + DIO-1 → multivalent capacity higher than DC (vac site + infection: iv)**
  - Protection in listeriosis, lung/cutaneous tuberculosis & pneumonia mice models



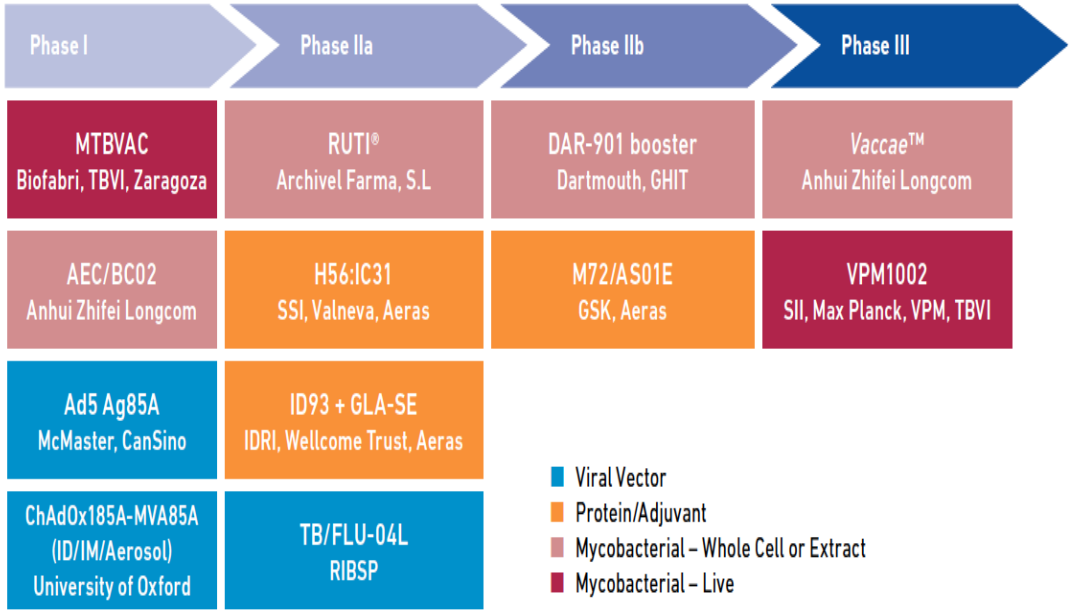
- GNP-$GAPDH_{1-15}$-LM vaccine:

→showed the highest multivalent protection ability

2. The product

c) Differential features facing the market (vaccination for adults)

1. **No available vaccine for listeriosis**
2. **No available vaccine for Mycobacteria** (cutaneous, lung or tuberculosis)
3. **Commercial vaccines for pneumonia**
   → lack of effects in adults
4. **Bacterial vaccines (MTB)**
   - attenuated mutants
   - Cell-wall extracts
   - Viral vectors

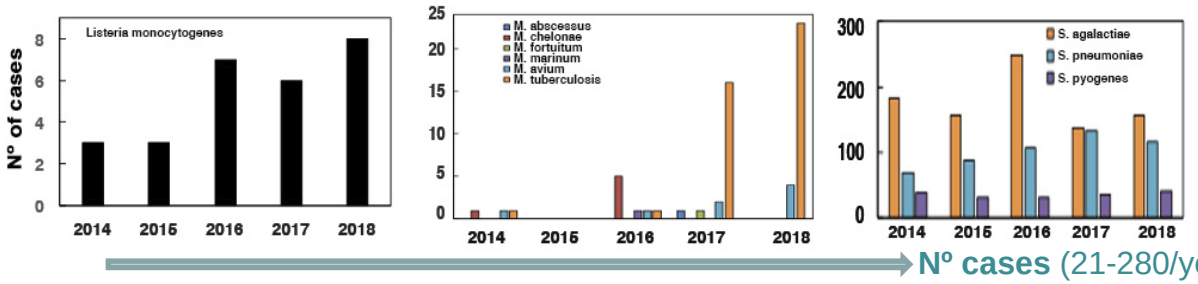


1. **Synthetic vaccine (peptide + gold-nanoparticle + adjuvant)**
2. **Multivalent vaccine able to protect against 3 different bacterial genus**

2. The product

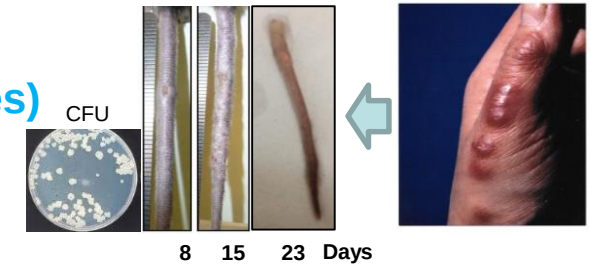
d) Current status of development

1.- Analysis of current status of infections in Cantabria & experiments in normal mice (C57BL/6) **(proof of concept)**



Meningitis (*L. monocytogenes*)

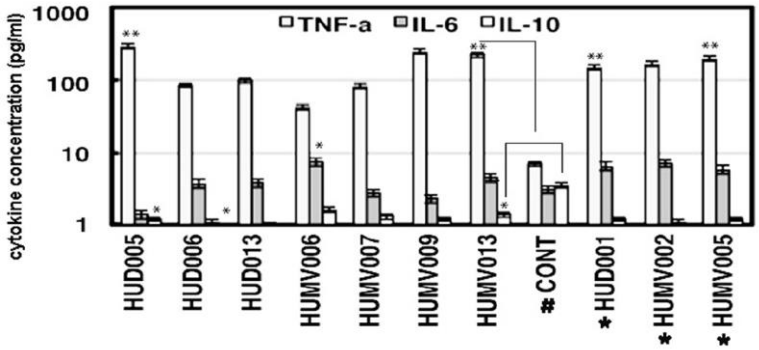
Nodal chain infection (*M. marinum*)



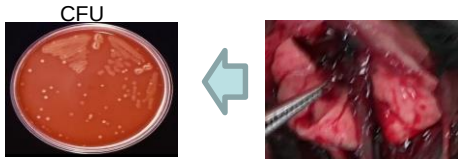
2.- Experiments in blood cells of patients-MoDC **(pre-clinical studies)**

- Human MoDC of patients with listeriosis

Incubation with GNP-GAPDH$_{1-15}$ induce a Th1 pro-inflammatory response (TH2 → TH1)



Lung disease (*S. agalactiae*)



- Human MoDC of patients with cutaneous mycobacteria
- Human MoDC of patients with *S. pneumoniae* or *agalact*

e) IPR protection

- A Spanish patent application was filed on 22nd June 2018 (ES filing number 201830628).
- On 13rd June 2019 an International patent application was filled (PCT/ES2019/070413) claiming priority of the Spanish patent application. The OEPM act as ISA (International Search Authority).
- The Search Report has already been partially positive considering only a relevant document from the research group.

2. The product

f) Pitfalls & Risks to be considered

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

2.- Missing immune biomarkers of protection in mice models & patients

3.- Missing *in vitro* effects of nanovaccines with human MoDC with other infections (tuberculosis & cutaneous mycobacteria, pneumonia)

4.- Missing *in vivo* experiments with immunodeficient mice (SCID, senescent mice: SAM1, SAMP1,8 o 10 o SAMR1)

3. Partnering opportunities

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

4. Questions

Funding requirement to finish Pre-clinical studies ? 500.000 €

Monetary needs for Phase I clinical assay ? ~ 1.000.000 €