OUTER MEMBRANE PROTEINS BASED VACCINES AGAINST SALMONELLA

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**Mexican Social Security Institute (IMSS)**

- Main health organisation in Mexico
- 80 million affiliates
- Large cohorts of patients
- Clinical Research
- Biobanks

**1,811 Medical Facilities**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Count</th>
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<tbody>
<tr>
<td>1st level</td>
<td>Preventive medicine, first contact and family medicine</td>
<td>1,499</td>
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<td>2nd level</td>
<td>Surgical and speciality medicine</td>
<td>275</td>
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<td>3rd level</td>
<td>High speciality medicine</td>
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Diseases produced by *Salmonella enterica*. GLOBAL HEALTH PROBLEM

**Salmonella enterica**
- Typhi
- Paratyphi A,B,C
- Typhimurium
- Enteritidis

**Typhoid Fever**
- 18-35 million
- 200,000 deaths

**Paratyphoid**
- 5.4 million

**Non-typhoidal Salmonellosis (NTS)**
- 94 million
- Mortality 20-25%

**Invasive NTS**

**Vaccines:**
- Ty21a
- Vi
- Vi-TT

**No vaccine**

Bahn MK et al., Lancet 2005
Mostly LMICs
MDR, XDR strains
WHO High priority for Vaccine development

Diseases produced by *Salmonella enterica*. GLOBAL HEALTH PROBLEM

Buckle GC, J Glob Health 2012
Majowicz, Clin Infect Dis 2010
S. Typhi porins are antigenic in Typhoid Fever patients

Typhoid Fever patients

S. Typhi outer membrane proteins


S. Typhi porins are strong immunogens able to induce protection against S. Typhi challenge

Active and passive protection 500 DL50
S. Typhi challenge in mice

Porin specific proliferative T cell responses in mice


Do porins induce long-lasting protective antibody responses?

ELISA titres

Bactericidal titres

Days after immunisation

Development of Porins based experimental vaccines against Typhoid Fever

PORINS

VI-PORINS
Faculty of Chemistry. UNAM

Armando Isibasi

John B. Robbins

VI-TETANUS TOXOID
Rodríguez-Anguiano RE. 1999
Master Degree Thesis
Faculty of Medicine UNAM

SIREVA
**S. Typhi** porins as experimental vaccine against Typhoid Fever

**ISIPOR Vaccine:**
- *Innocuous*
- *Pyrogens free*

Patent No. MX346872

Safe and well tolerated vaccine

IgM-IgG seroconversion

Immunogenic vaccine

T cell proliferation IFNg+

Phase 1 clinical trial

**S. Typhi** porins induce long-lasting IgM and IgG Ab responses in humans (11 years)

Salmonella Porins
Responses in healthy donors

Why porins are strong immunogens?

Prof. Burkhard Ludewig
Kantonsspital St. Gallen CH

N. Valero-Pacheco, J. Blight, et al., submitted
Porins are agonist of TLR2 and 4 and induced an adjuvant effect on the antibody responses to co-immunised vaccines

HEK293 cells

TLR 2

Porins

Vi polysaccharide anti-Typhoid vaccine

Vi + Porins

Vi

Vi + PorK

Pandemic influenza inactivated virus

HAI titre

Patent MX292850. 18/08/2011

Pérez-Toledo, et al., Front Immunol, 2017
• **Porins vaccine is safe, well tolerated and immunogenic in humans**

• 1 dose induced a long-lasting (11 years) antibody responses in humans

• Shared T cell epitopes among clinically relevant strains may maintain T cell responses for long time

• Intrinsic adjuvant properties of porins could promote long-lasting responses to itself and co-immunised antigens
Who is responsible for the induction of protection?

Prof. Adam Cunningham
University of Birmingham UK
In HIV patients, anti-LPS Ab block bactericidal anti-porins Ab

MacLennan, et al. Science 2010

Perspectives
S. Fauci. Science 2010

The porin OmpD from non-typhoidal *Salmonella* is a key target for a protective B1b cell antibody response

**Inmunisation**

*S. Typhimurium* (STm) Porins (OmpC, OmpF, OmpD)

**STm Challenge**

- STm OmpD+
- STm OmpD-
- STm OmpR- OmpD+

Bactericidal antibodies

*Gil-Cruz, et al. PNAS 2009*
Modelling reveals the limited access O chain allows to the cell surface

Adam Cunningham, Vas Bavro, et al.
Model of anti-OmpD porin Ab induction of protection

Adam Cunningham, Vas Bavro, et al.
Development of a multivalent vaccine against the diseases produced by *Salmonella enterica*

Typhoid Fever
Paratyphoid Fever
Non-typhoidal Salmonellosis (NTS)
Invasive NTS

ANTI-SALMONELLA MULTIVALENT VACCINE

Patent application
MX/a/2015/017677
ACKNOWLEDGEMENTS
MEDICAL RESEARCH UNIT ON IMMUNOCHEMISTRY

Dr. Armando Isibasi Araujo.
Emeritus Professor IMSS

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ACKNOWLEDGEMENTS

Instituto de Biotecnología, UNAM
Dr. Edmundo Calva

Unidad de Medicina Experimental, FM, UNAM
Dr. Ingeborg Becker

Escuela Nacional de Ciencias Biológicas, IPN
Dr. Mayra Pérez Tapia

Facultad de Química UNAM
Dr. Rodolfo Pastelin
Dr. Mario Moreno Eutimio

Rutgers University:
Nuriban Valero Pacheco

University of Birmingham UK:
Prof. Adam Cunningham
Prof. Calman MacLennan
Dr. Marisol Pérez-Toledo

Institute of Immunobiology, Saint Gallen, Switzerland:
Prof. Burhard Ludewig
Dr. Cristina Gil-Cruz
Dr. Christian Pérez Shibayama

University of Oxford, UK:
Prof. Paul Kleneman
Dr. Arturo Reyes-Sandoval

Emory University:
Dr. Luisa Cervantes Barragán