KEY IMMUNOLOGICAL CONSIDERATIONS FOR LEISHMANIASIS VACCINE DEVELOPMENT

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• 100 endemic countries

• Annual incidence: 1-2 Million cases
Visceral leishmaniasis

- Slow life-curing disease (3 to 18 months)
- Disfigurement
- Stigma
- Disappointing TTT

Cutaneous leishmaniasis

PUBLIC HEALTH PROBLEM
Active lesion or asymptomatic infection

Resistance to subsequent reinfection
The macrophage at the center of the immunity against Leishmaniasis
These two pathways have been extensively defined in experimental inbred mice.
Increasing immunity

Increasing severity

Low force of infection
Increasing immunity

High force of infection

Increasing severity
The tissue damage and clinical severity depends also on immune responses directed against the parasite.
Doubtful extrapolation
Barriers to successful development of a human vaccine

1. Difficulty of extrapolation and over-dependence on animal models
Candidates of vaccines
Leishmaniasis vaccine development over years

- Full range of antigens identified by a full range of techniques (from the use of serology through to computational prediction)

- Almost all conceivable vaccine delivery strategies
Strategies for the development of anti-Leishmania vaccines

## Four candidate vaccines to or near to the clinic

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Description</th>
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<tbody>
<tr>
<td>A recombinant fusion protein delivered with strong Th1-inducing adjuvants</td>
<td>(LEISHF3+ GLA-SE)</td>
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<tr>
<td>A naked multi-epitope DNA vaccine</td>
<td>(LeishDNAvax)</td>
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<tr>
<td>An adenovirus-based vaccine</td>
<td>(ChAd63-KH)</td>
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<tr>
<td>A live genetically attenuated vaccine</td>
<td>(L. major/L. donovani centrin-)</td>
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</table>
Vaccination

**Objectif**

Formulation of an anti-leishmaniasis vaccine composed of 1 or 2 parasite antigens with 1 to 2 salivary components.
Efficacy of immunization against vector saliva

Balb/c

Naïve mice

Pre-exposed mice

IFN-γ/IL-12 Response

Resistance to infection
Reed SG et al, 2015
Potentiel candidates
To test the mRNA vaccine formulation of different candidates of vaccine

PI: Thouraya Boussoffara
SELECTION OF ANTIGENS

One sand fly salivary protein

4 Leishmania antigens

- Conserved between different Leishmania species
- Inducing a Th1 cell response
- Immunogenic in humans
- Well presented by APC

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**IMMUNOGENICITY**

- Leish-Pr1 (dose 1/dose2)
- Leish-Pr2 (dose 1/dose2)
- Leish-Pr3 (dose 1/dose2)
- Leish-Pr4 (dose 1/dose2)
- SFS-Pr1 (dose 1/dose2)
- PBS

(n=8/group)

- 0 weeks
- 3 weeks
- 7 weeks

**Serum** → Ags-specific IgG/ IgG1/ IgG2a

**Spleen** →

- In vitro stimulation
  - NS
  - LmF/T
  - ConA
  - rPr

  - Lymphoproliferation (BrdU)
  - IFN-γ, IL-12p70, IL4, IL-10 and GrzB (ELISA)

*Optimal dose for each construct*
Promising results
**Efficacy**

Challenger (ear) (1000 L.major + 0.2 HGS P. papatas) **Lesion size**

- **Weeks Post-Challenge**
  - 0
  - 3
  - 7

**IM**

- **Leish-Pr1 (+/- SFS-Pr1)**
- **Leish-Pr2 (+/- SFS-Pr1)**
- **Leish-Pr3 (+/- SFS-Pr1)**
- **Leish-Pr4 (+/- SFS-Pr1)**
- **SFS-Pr1**
- **PBS**

**Parasite Load** (Limiting dilution Assay)

**Ags-specific IgG/IgG1/IgG2a** (SLA/ rSFS-Pr1)

**T cells producing IFN-γ, IL-2, TNF-α (FACS)**

**LEGENDplex™ MU Th Cytokine Panel (Th1/Th2/Th17)**

**GrzB production (ELISA)**

**Ear**

**dLN**

**Serum**

**Spleen**

**Institut Pasteur de Tunis**
Immunogenicity in humans (Ex vivo)

20 LCZ individuals

10 healthy controls

RANKING