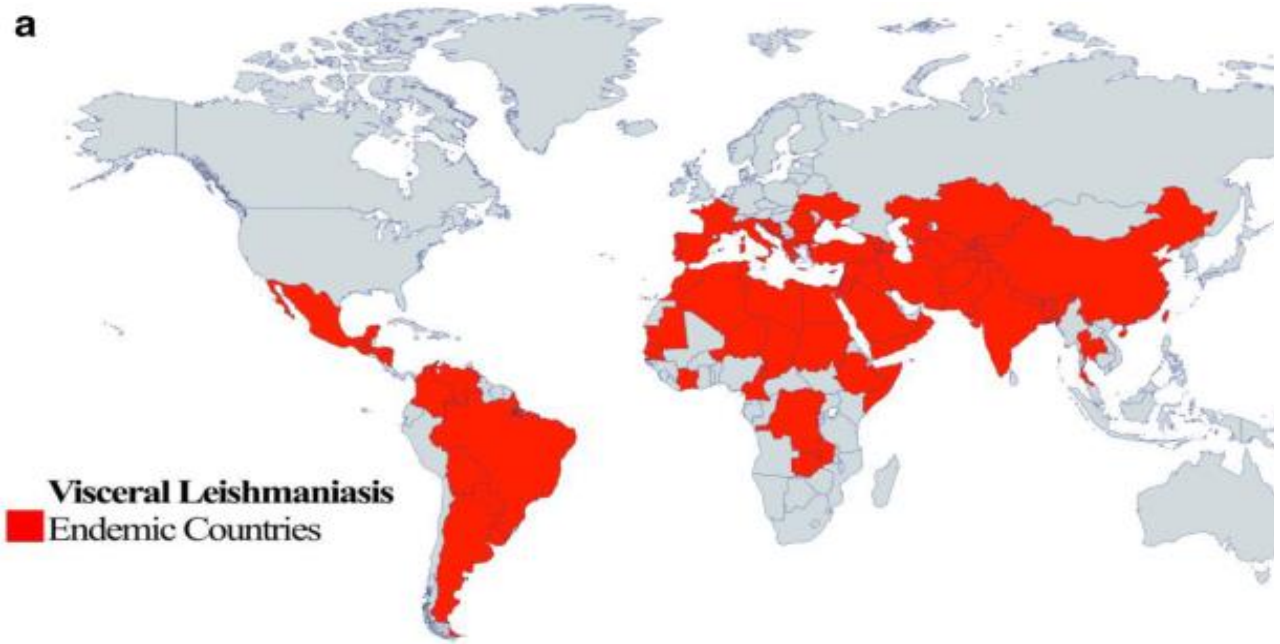
Institut Pasteur de Tunis, Tunisia

KEY IMMUNOLOGICAL CONSIDERATIONS FOR LEISHMANIASIS VACCINE DEVELOPMENT

Mélika Ben Ahmed, MD, PhD



- 100 endemic countries

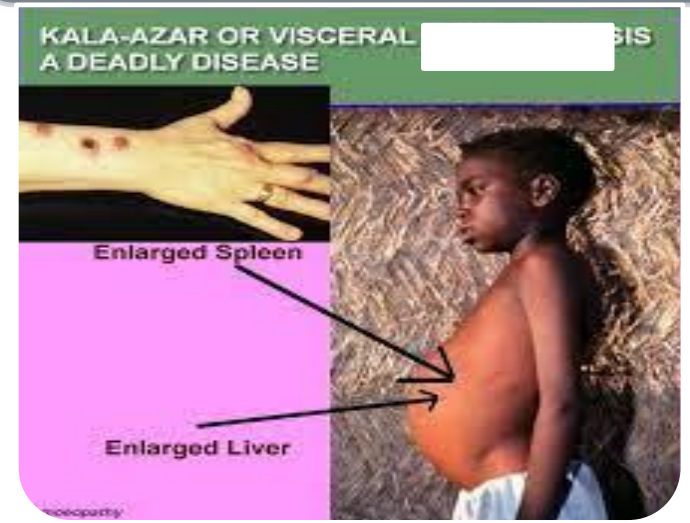
- Annual incidence: 1- 2 Million cases

Sasidharan S. Parasitolgy research (2021)

PUBLIC HEALTH PROBLEM

Visceral leishmaniasis

Cutaneous leishmaniasis



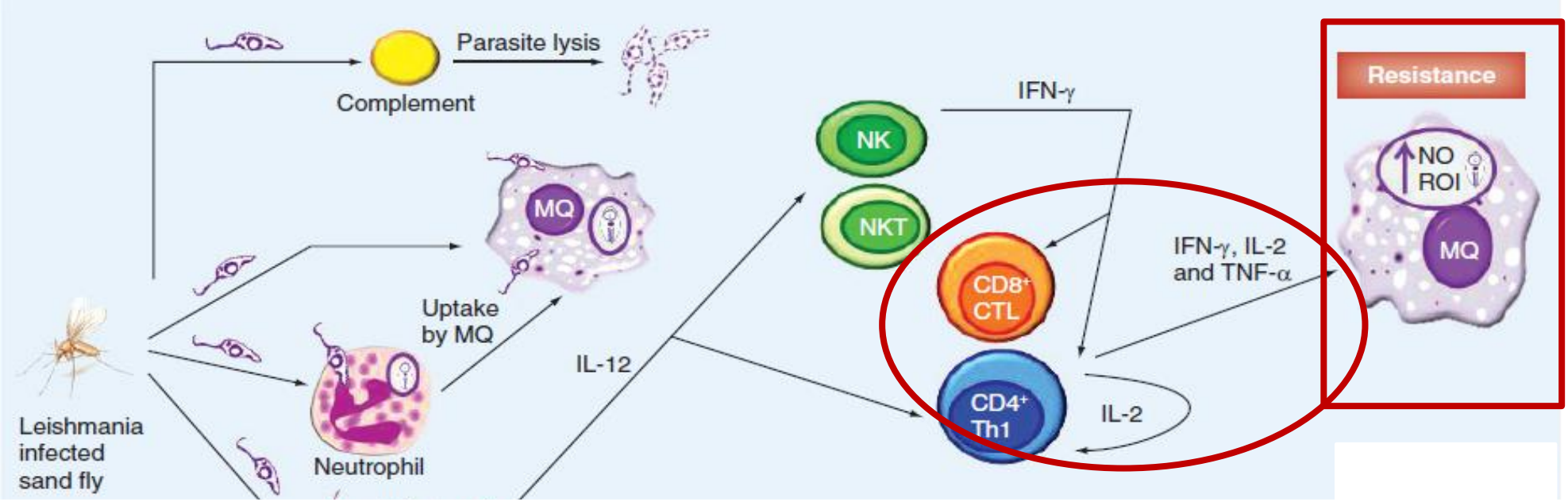
- Slow life-curing disease (3 to 18 months)
- Disfigurement
- Stigma
- Disappointing TTT

Vaccination

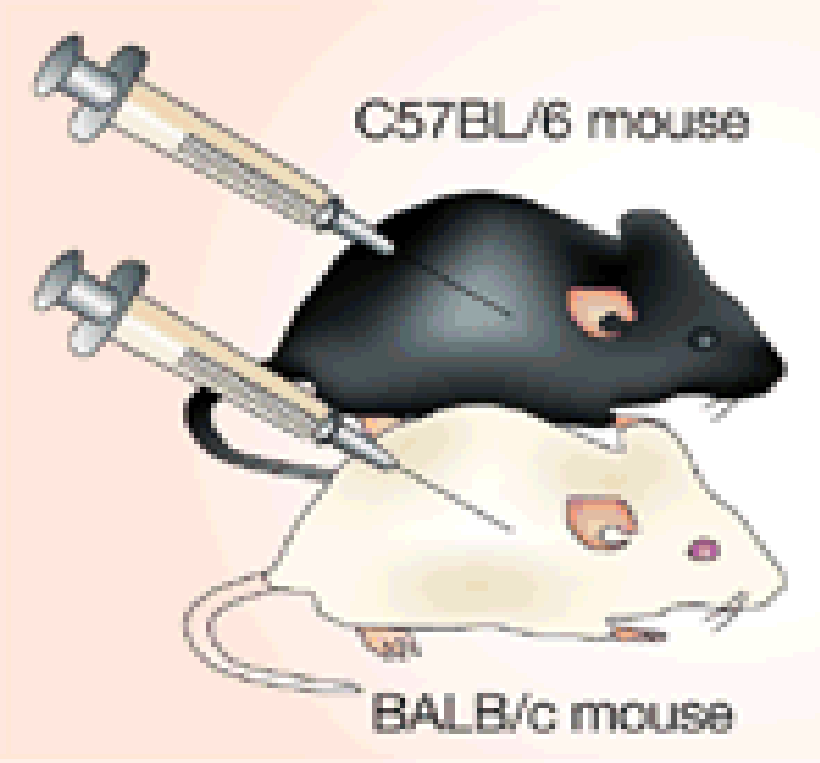
Active lesion or asymptomatic infection

Resistance to subsequent reinfection

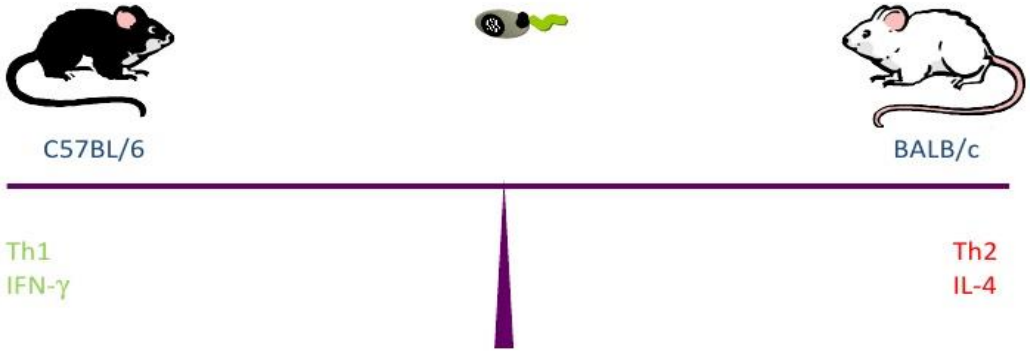
The macrophage at the center of the immunity against Leishmaniasis



These two pathways have been extensively defined in experimental inbred mice



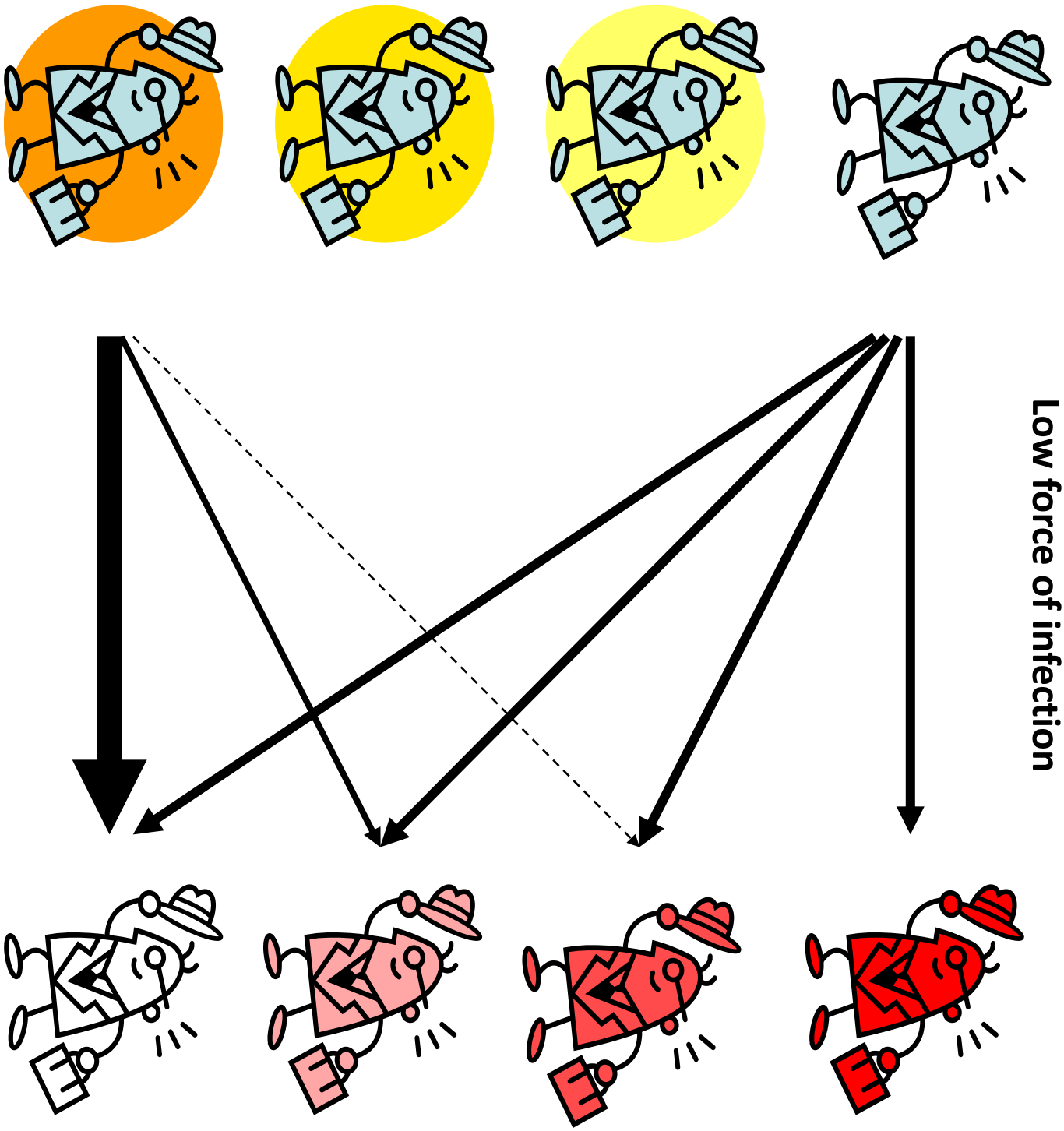
Th1/Th2 paradigm



BUT

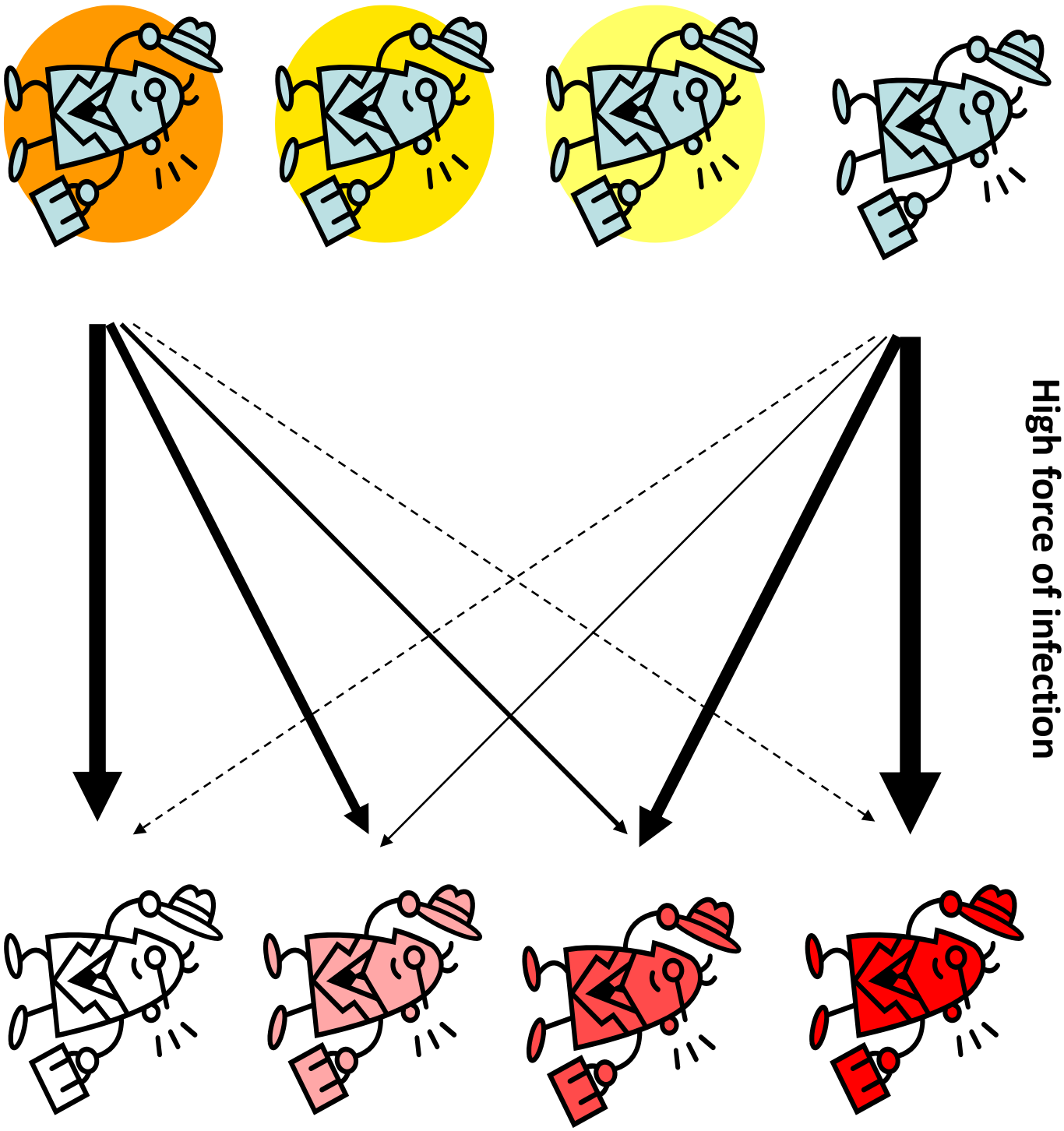
Mixed profile in humans

Increasing immunity



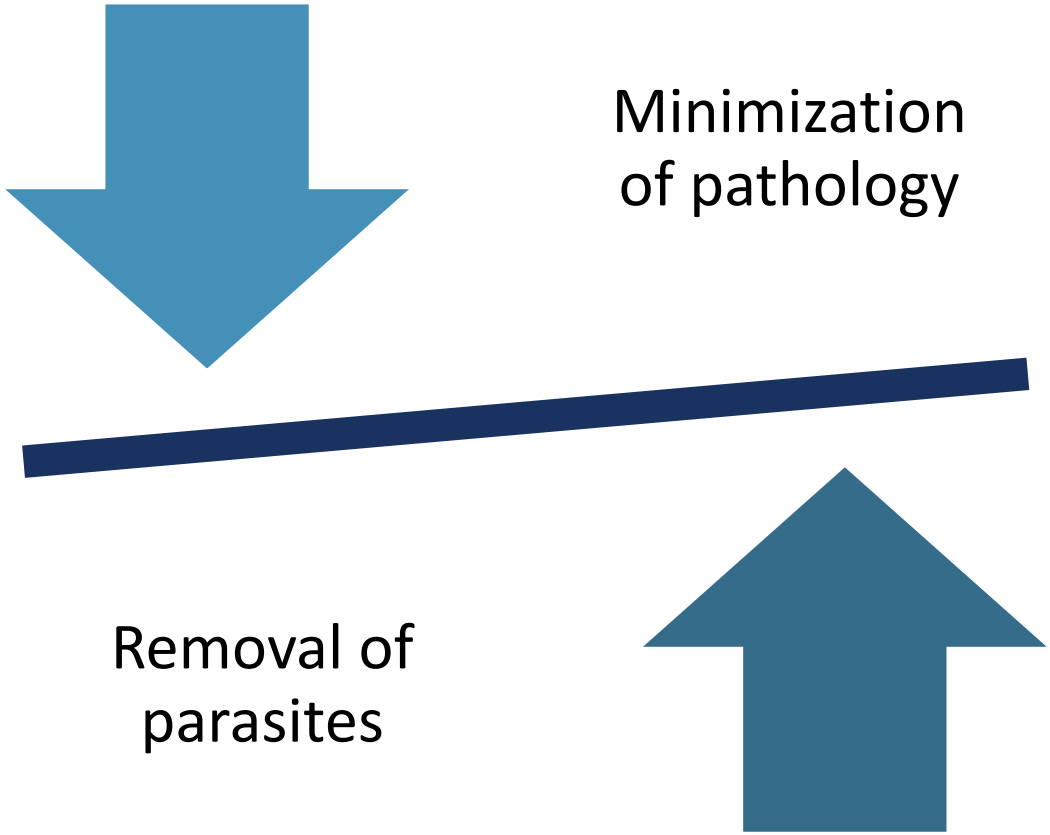
Increasing severity

Increasing immunity

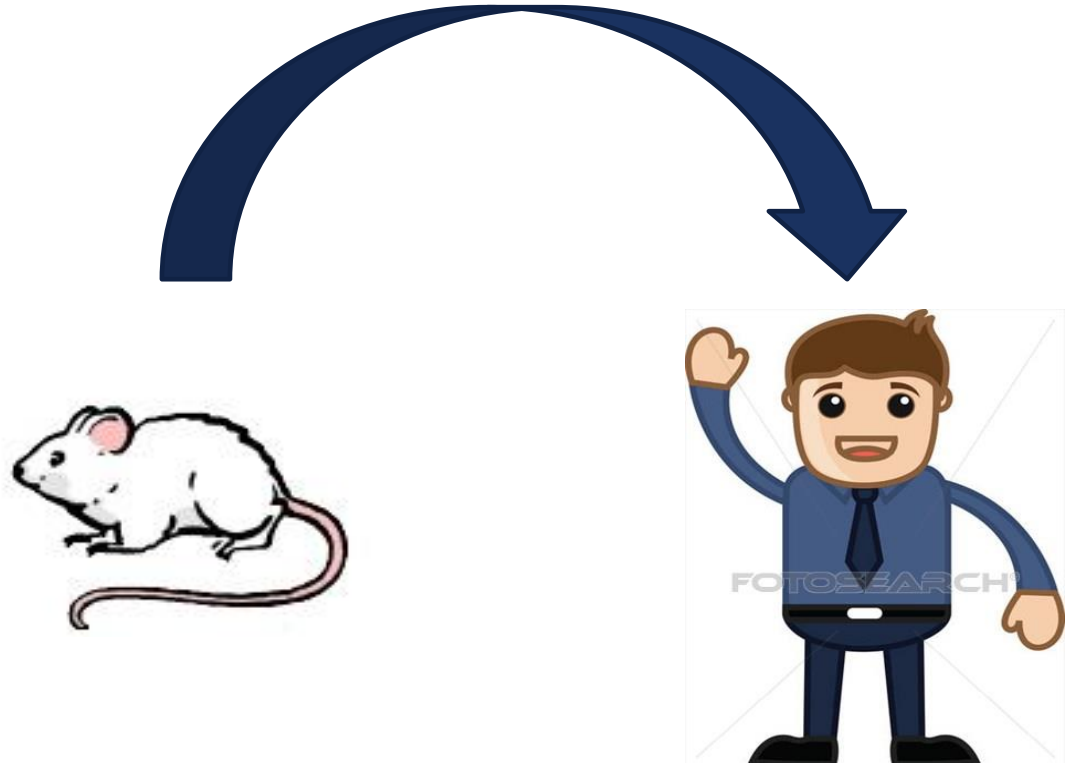


Increasing severity

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

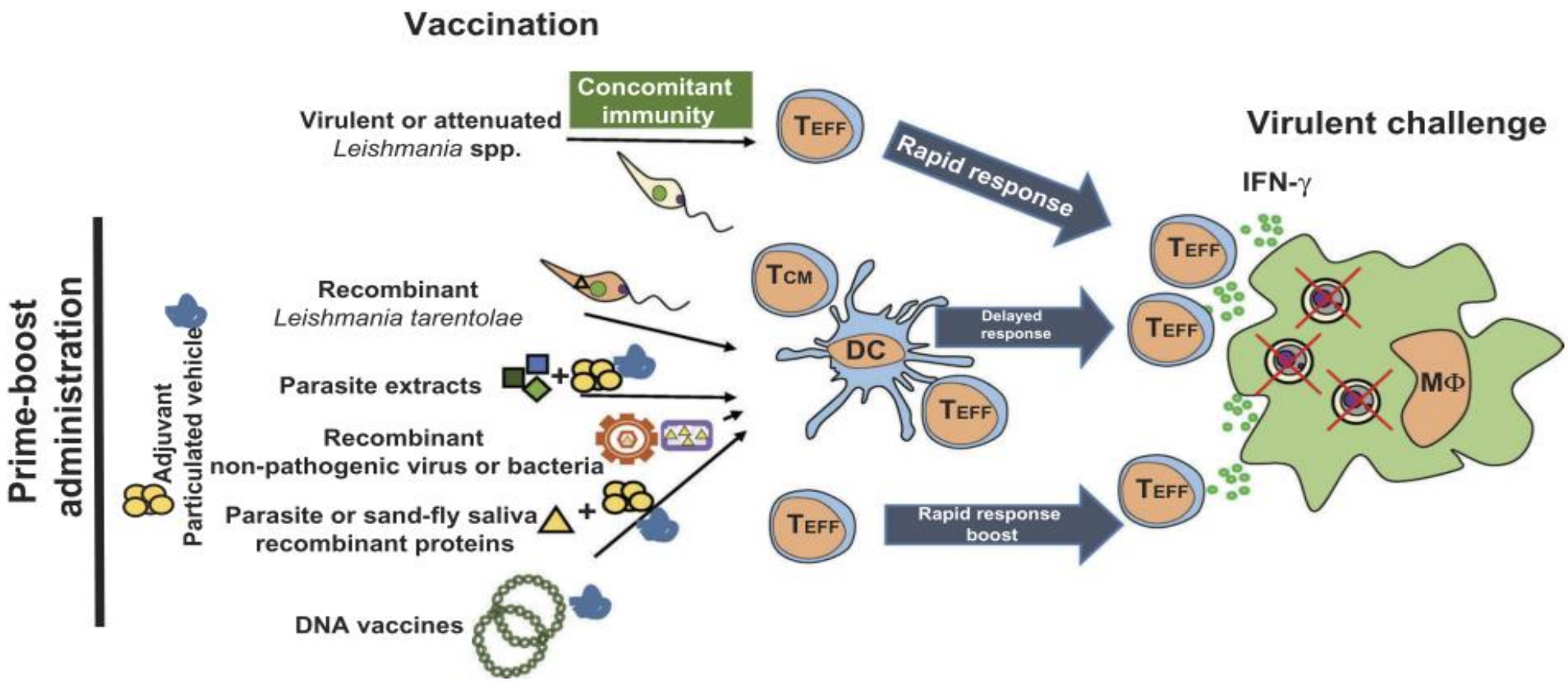
Candidates of vaccines

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



Iborra S, Expert Revie of Vaccines, 2018.

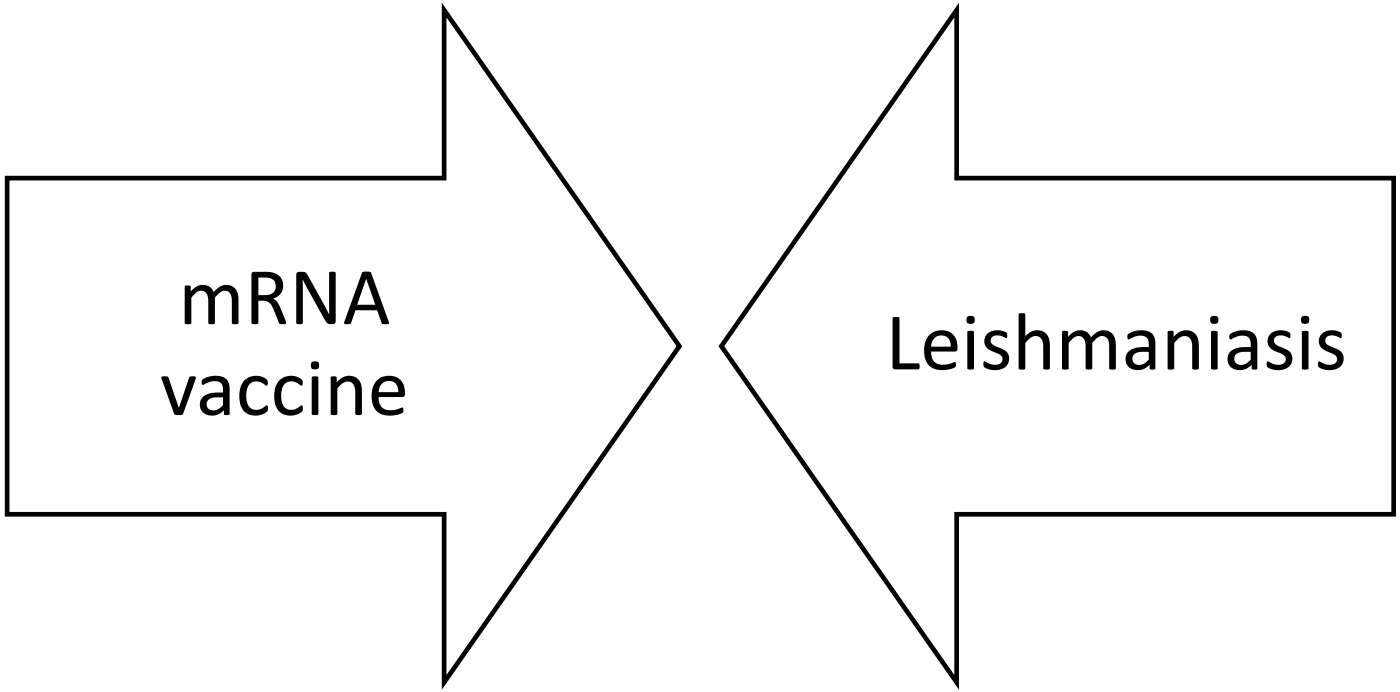
Four candidate vaccines to or near to the clinic

A recombinant fusion protein delivered with strong Th1-inducing adjuvants **(LEISHF3+ GLA-SE)**

A naked multi-epitope DNA vaccine **(LeishDNAvax)**

An adenovirus-based vaccine **(ChAd63-KH)**

A live genetically attenuated vaccine **(L. major/L. donovani centrin–)**

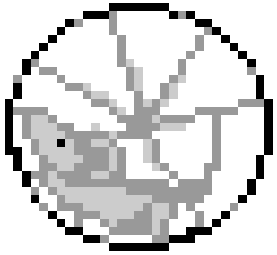

mRNA
vaccine
Leishmaniasis

Vaccination

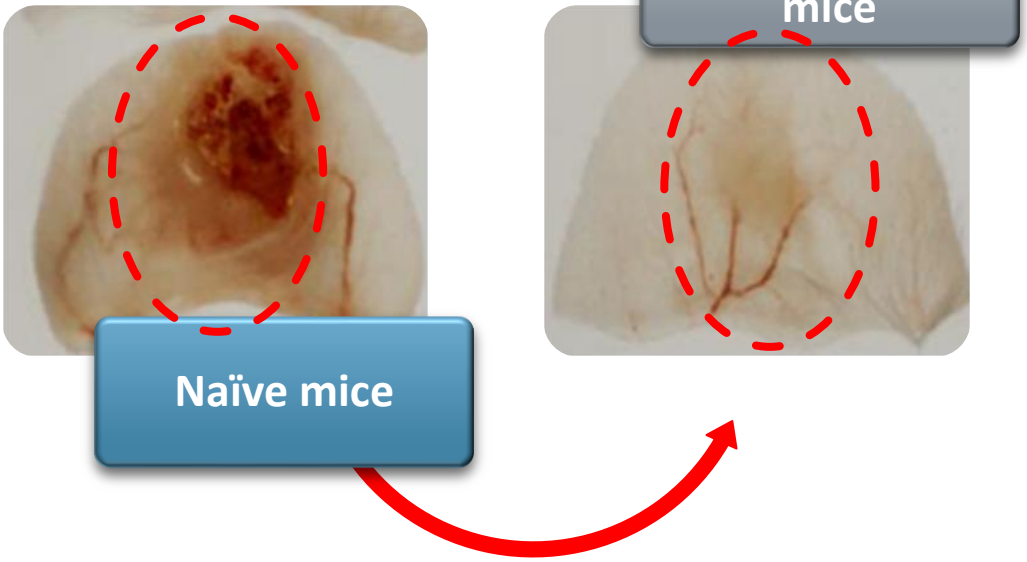
Objectifve

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

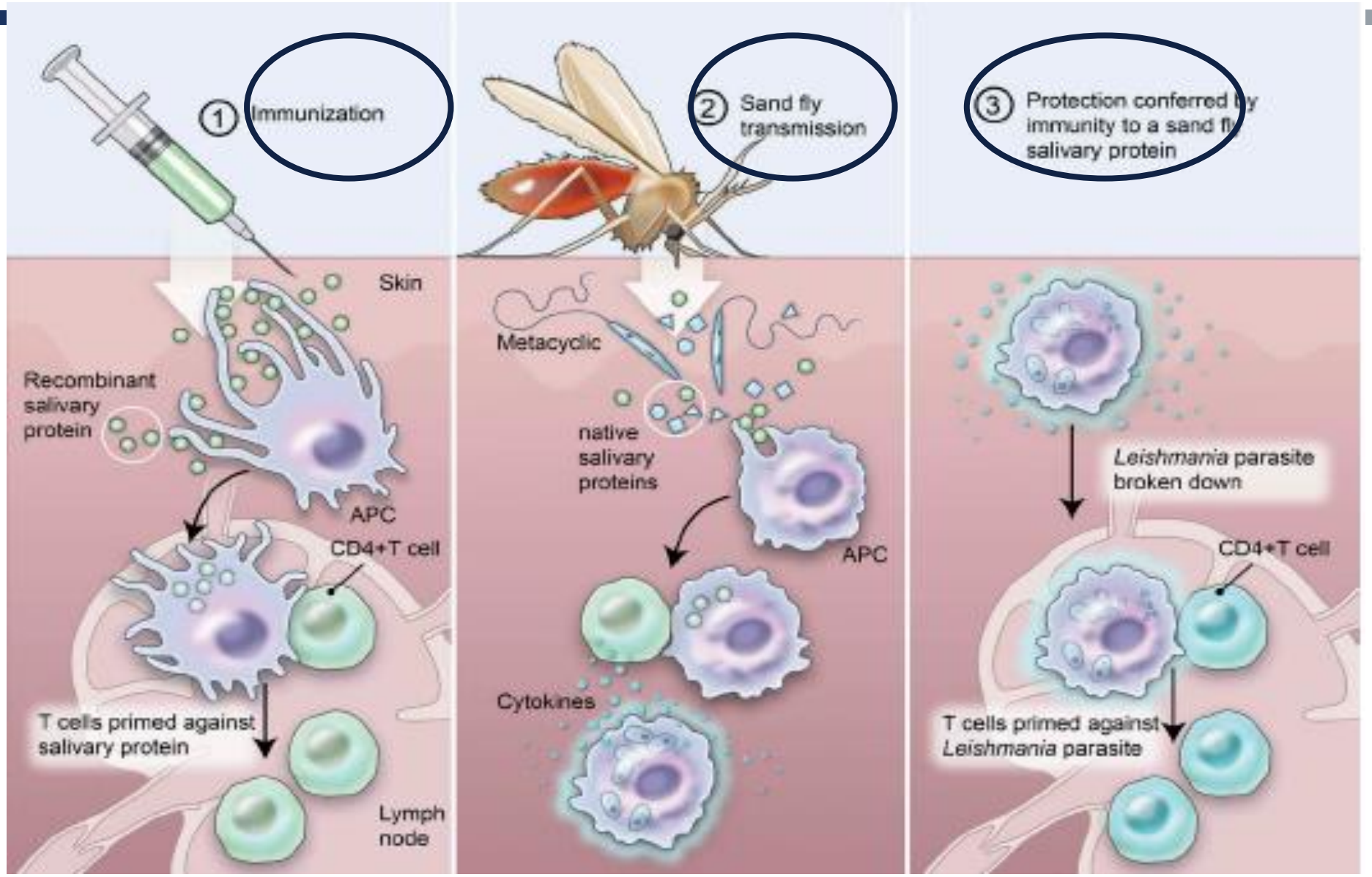


BALB/c



IFN-γ/IL-12 Response

Resistance to infection



Reed SG et al, 2015

Published in final edited form as:
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Phlebotomus papatasi Yellow-Related and Apyrase Salivary Proteins Are Candidates for Vaccination against Human Cutaneous Leishmaniasis

Aymen Tlili[1], Soumaya Marzouki[1], Emna Chabaane[1], Maha Abdeladhim[2], Wafa Kammoun-Rebai[3], Rahma Sakkouhi[1], Nabil Belhadj Hmida[1], Fabiano Oliveira[2], Shaden Kamhawi[2], Hechmi Louzir[1,4], Jesus G. Valenzuela[2], and Mélika Ben Ahmed[1,4]

Updating the Salivary Gland Transcriptor
Phlebotomus papatasi (Tunisian Strain):
Sand Fly-Secreted Immunogenic Protei

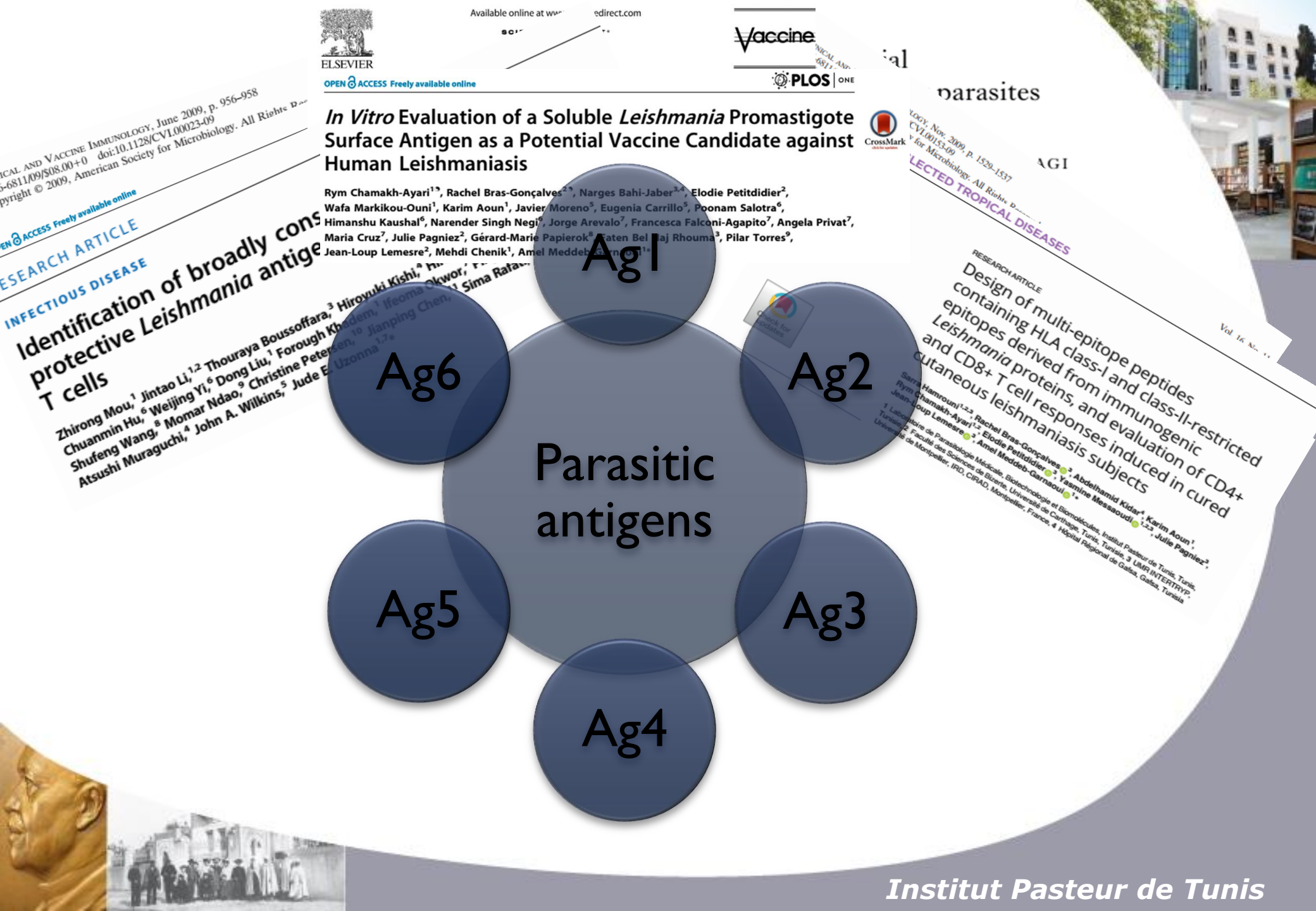
Maha Abdeladhim[1,3], Ryan C. Jochim[2,3], Melika Ben Ahmed[1,3], Elyes Zhioua[1], Saifedine Cherni[4], Hechmi Louzir[1,3], José M. C. Ribeiro[5], Jesus G. Valenzuela[2,*]

Immune Response to the Saliva of
papatasi Is Mediated by IL-10-Producing
Cells and Th1-Polarized CD
hocytes

Maha Abdeladhim[1,3], Mélika Ben Ahmed[1,*,3], Boussoffara[2], Nabil Belhaj Hamida[3], Thouraya nida[1],

PLOS NEGLECTED TROPICAL DISEASES

Potentiel candidates


Ag1
Ag2
Ag3
Ag4
Ag5
Ag6
Parasitic antigens
Vaccine
PLOS ONE
In Vitro Evaluation of a Soluble Leishmania Promastigote Surface Antigen as a Potential Vaccine Candidate against Human Leishmaniasis
Identification of broadly cons protective Leishmania antige T cells
parasites
Design of multi-epitope peptides containing HLA class-I and class-II-restricted epitopes derived from immunogenic Leishmania proteins, and evaluation of CD4+ and CD8+ T cell responses induced in cured cutaneous leishmaniasis subjects
Institut Pasteur de Tunis

To test the mRNA vaccine formulation of different candidates of vaccine

PI: Thouraya Boussoffara

IPT
معهد باستور تونس Institut Pasteur de Tunis

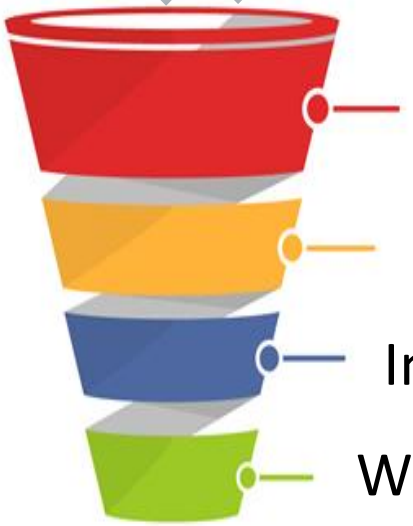
moderna

BIOMÉRIEUX

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

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

Serum ➡ Ags-specific IgG/ IgG1/ IgG2a

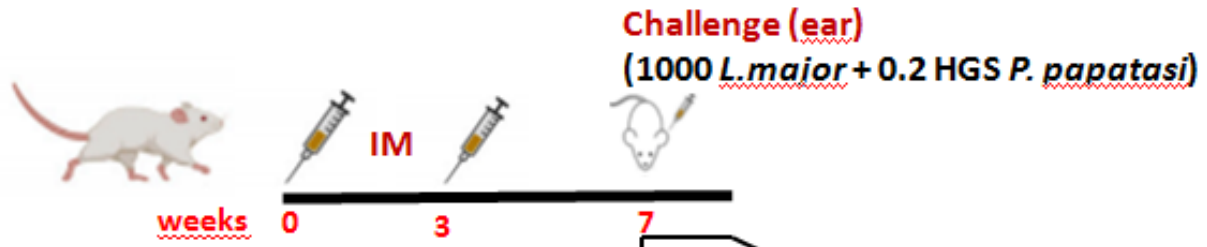
Spleen ➡ *In vitro* stimulation
NS *LmF/T* ConA *rPr*

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

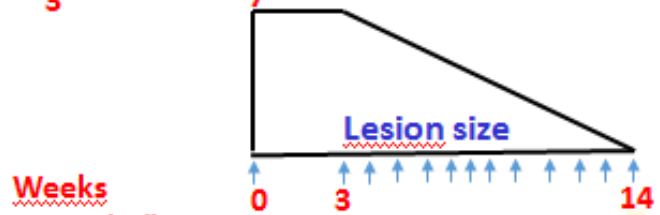
Optimal dose for each construct

Promising results

EFFICACY



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



Parasite Load
(Limiting dilution Assay)

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

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

GrzB production (ELISA)

* *Lm*F/T
* ConA
* *r*SFS-Pr1

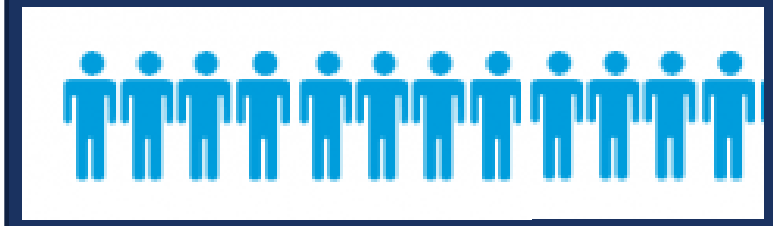
Spleen

Serum

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

Immunogenicity in humans
(*Ex vivo*)

20 LCZ individuals



10 healthy controls

RANKING