

The role of candidate vaccines in VL elimination

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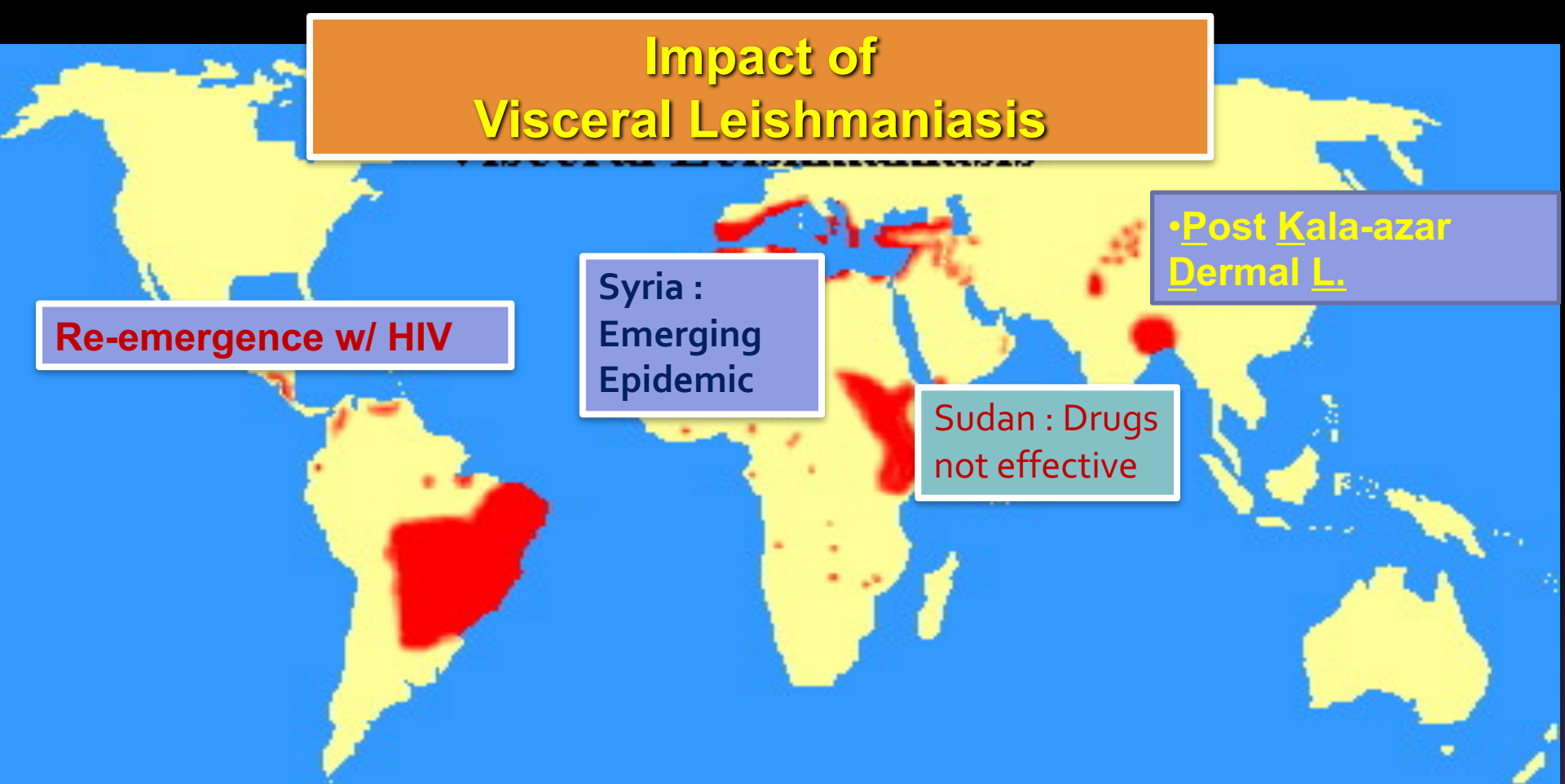
Former DG ICMR

➤ NEED FOR VACCINE?

- Many endemic areas have not yet achieved optimal control due to logistical, biological as well as technical challenges.
- Institutional treatment regimens are now provided: Adverse reactions and drug resistance is major problem.
- The number of cases are coming down the need of hour is an effective vaccine to sustained elimination by stopping intra-familial and intercommunity transmission of disease from asymptomatic cases & PKDL patients
- Many patients do reach the caregiver in remote areas : vaccination becomes best solution.



Impact of Visceral Leishmaniasis



VL Fact sheet

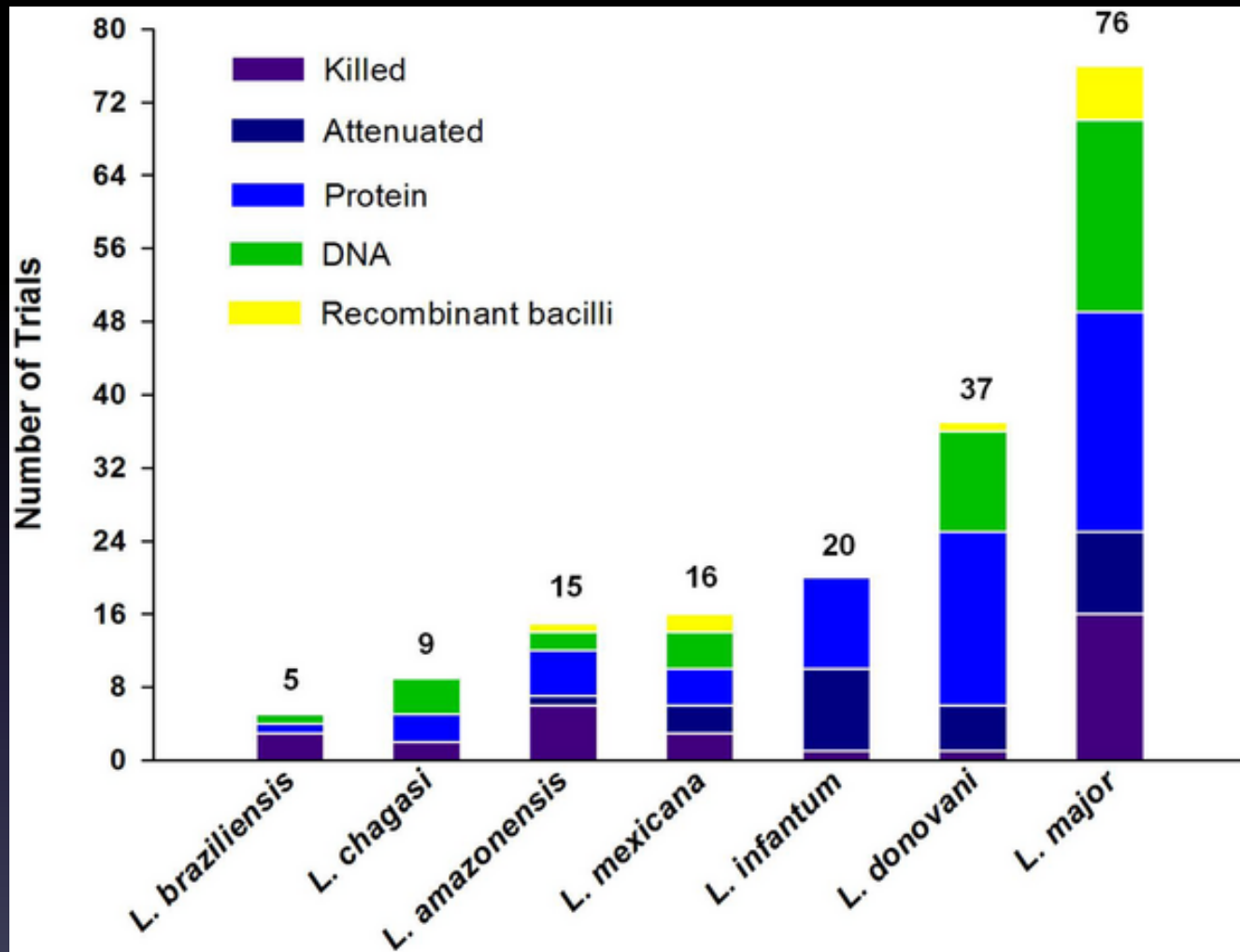
200 Million
People currently at risk for contracting VL

62
Countries endemic with VL

500,000
New cases per year

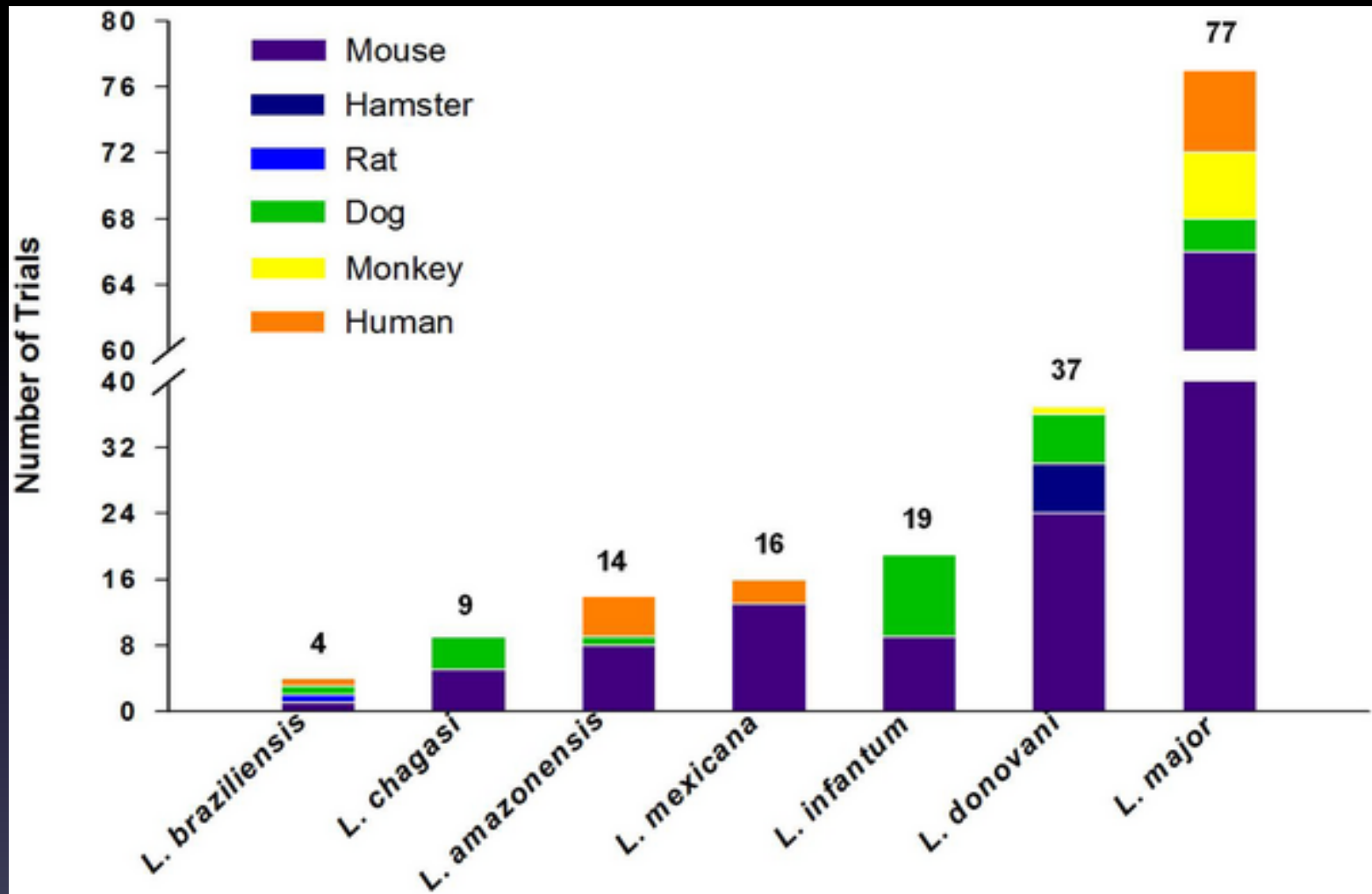


Figure . Profile of strategies used in leishmaniasis trials.



Costa CHN, Peters NC, Maruyama SR, de Brito EC Jr, de Miranda Santos IKF, et al. (2011) Vaccines for the Leishmaniasis: Proposals for a Research Agenda. PLoS Negl Trop Dis 5(3): e943. doi:10.1371/journal.pntd.0000943
<http://journals.plos.org/plosntds/article?id=info:doi/10.1371/journal.pntd.0000943>

Figure . Animal models used in leishmaniasis trials.



Costa CHN, Peters NC, Maruyama SR, de Brito EC Jr, de Miranda Santos IKF, et al. (2011) Vaccines for the Leishmaniasis: Proposals for a Research Agenda. PLoS Negl Trop Dis 5(3): e943. doi:10.1371/journal.pntd.0000943
<http://journals.plos.org/plosntds/article?id=info:doi/10.1371/journal.pntd.0000943>

SUBUNIT VACCINES



Today there are almost 30 different characterized proteins, out of at least 8000 proteins encoded in the parasite genome, for vaccine studies.

Leishmune^R is a subunit Canine Vaccine licensed and in use in dogs against VL in Brazil,
(although it does not work in humans)
It is a purified *L. donovani* fraction, named fructose mannose ligand (FML)
and a saponin adjuvant



The advertisement features a black and white Chihuahua dog sitting on a yellow background, holding an orange fly swatter. Several flies are shown flying around the dog. To the right of the dog, the text reads: "Leishmune^R", "A primeira vacina com...", "Já existe mais eficiente para seu cão leishman...", and "Seus felizes e saudáveis momentos". Below this text is the Fort Dodge logo and the Pfizer Saúde Animal logo, with the tagline "uma empresa do grupo Pfizer".

Leishmune^R
A primeira vacina com...

Já existe mais eficiente para seu cão leishman...

Seus felizes e saudáveis momentos

FORT DODGE

Pfizer Saúde Animal
uma empresa do grupo Pfizer

Contém 10 frascos de vacina liofilizada acompanhados de 10 frascos de diluente

LEISHMUNE
Vacina contra Leishmaniose Visceral Canina
Uso Veterinário

FORT DODGE

Proprietário e Fabricante:
FORT DODGE Saúde Animal Ltda.
Rua Luiz Fernando Rodrigues, 1701
CEP 13064-798 - Campinas - SP
CNPJ 43.588.045/0001-31
Resp. Tec. Dr. B. O. A. de Oliveira
CRMV-SP nº 2925
SAC 800-761981
www.fortdodge.com.br

Licenciado ao Ministério da Agricultura nº 0 e nº 8.627 em 11/06/03

Instruções completas: vide bula

Precauções:
Conservar entre 2°C e 8°C, ao abrigo da luz solar. Evitar congelamento. Agitar bem antes de usar.

Venda sob prescrição obrigatória e utilização sob supervisão do Médico Veterinário.

LEISHMUNE
Oftumir
Uso Veterinário

LEISHMUNE
Oftumir
Uso Veterinário

Vaccines such as Leish-F₁, F₂ and F₃, developed at IDRI and designed based on selected *Leishmania* antigen epitopes, have been in clinical trials

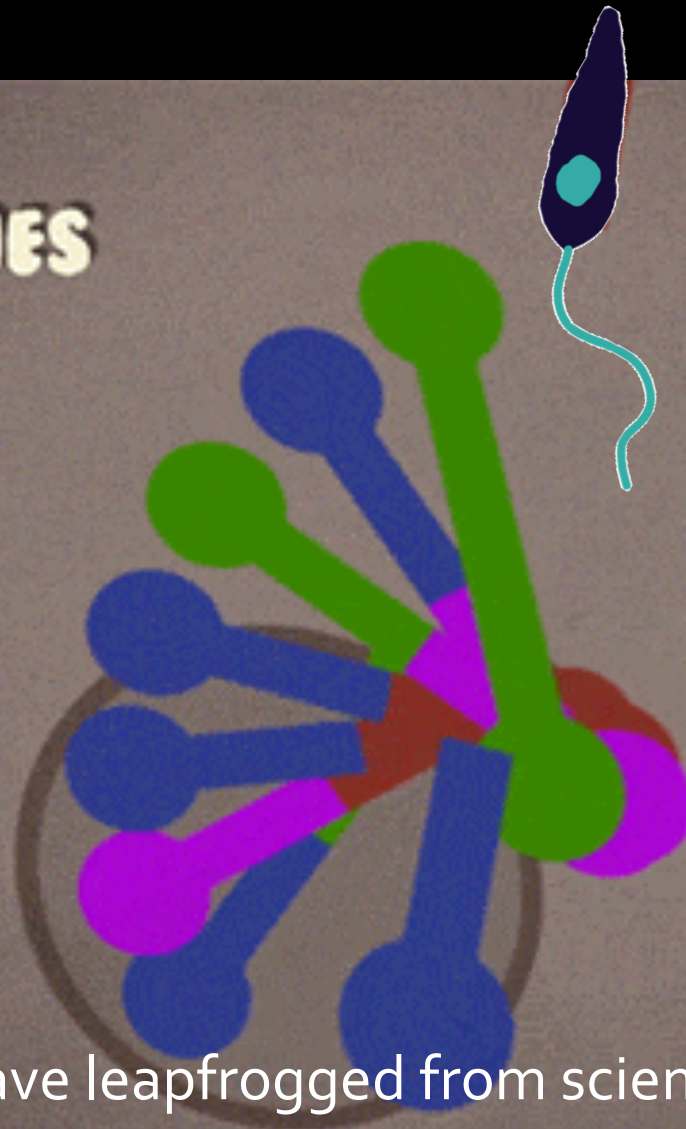
From mouse to man: safety, immunogenicity and efficacy of a candidate leishmaniasis vaccine LEISH-F3+GLA-SE

[Rhea N Coler](#),^{1,*} [Malcolm S Duthie](#),¹ [Kimberly A Hofmeyer](#),¹ [Jeffery Guderian](#),¹ [Lakshmi Jayashankar](#),¹ [Julie Vergara](#),¹ [Tom Rolf](#),¹ [Ayesha Misquith](#),¹ [John D Laurance](#),¹ [Vanitha S Raman](#),¹ [H Remy Bailor](#),¹ [Natasha Dubois Cauwelaert](#),¹ [Steven J Reed](#),¹ [Aarthi Vallur](#),¹ [Michelle Favila](#),¹ [Mark T Orr](#),¹ [Jill Ashman](#),¹ [Prakash Ghosh](#),² [Dinesh Mondal](#),² and [Steven G Reed](#)¹

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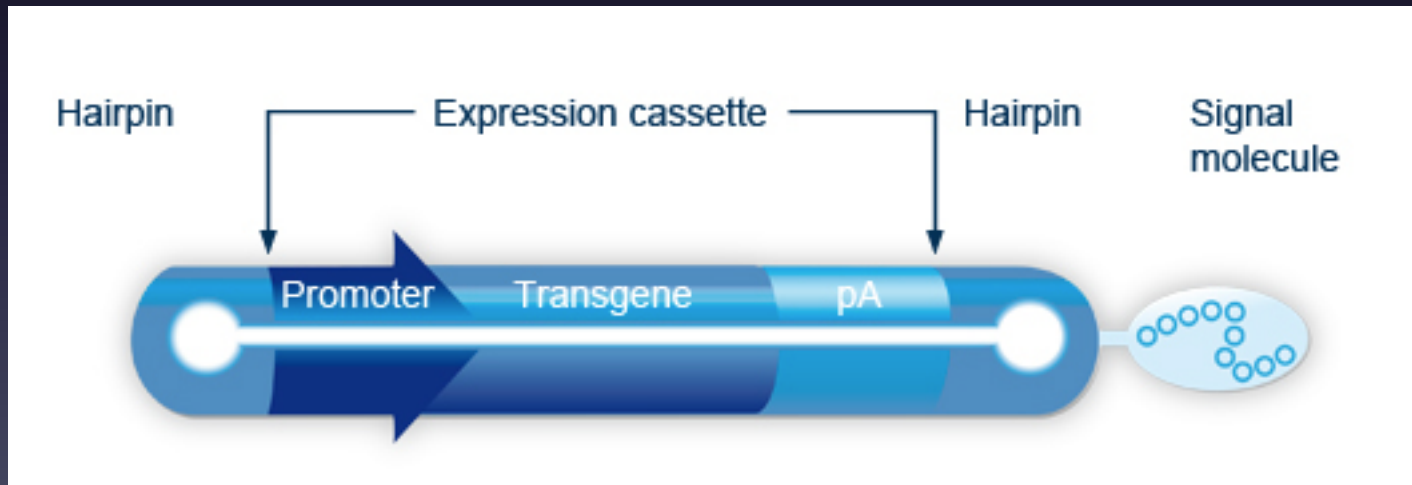
They report results for a first-in-human study that evaluated LEISH-F3+GLA-SE in healthy adults from a non-endemic region (in US). Immunization in a human clinical trial proved to be safe and highly immunogenic; in immunized subjects, they observe a substantial anti-LEISH-F3 serum antibody response and production of key protective cytokines by LEISH-F3-recalled peripheral blood mononuclear cells (PBMCs), which may be potent contributors to vaccine efficacy.

DNA VACCINES



DNA vaccines have leapfrogged from scientific curiosity to one of the most dynamic fields of research and may offer new alternatives for the control of infectious diseases.

LEISHDNAVAX is a mixture of five MIDGE-Th1 vectors each encoding a different Leishmania antigen: KMP11, CPA, CPB, P74 (elongation factor 1-alpha) or TSA.²² Antigen selection and sequence design followed a novel rational approach. In a series of animal experiments it was demonstrated that LEISHDNAVAX is immunogenic and effective against challenge with Leishmania donovani, the causative agent of VL.²² The vaccine is aimed to be administered to humans in both preventive and therapeutic settings.



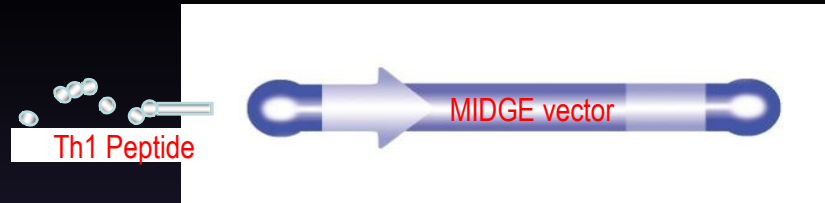
LEISHDNAVAX

Prevention and therapy of all forms of leishmaniasis

(Dr Christiane Juhls)

Vaccine: No clinical studies yet

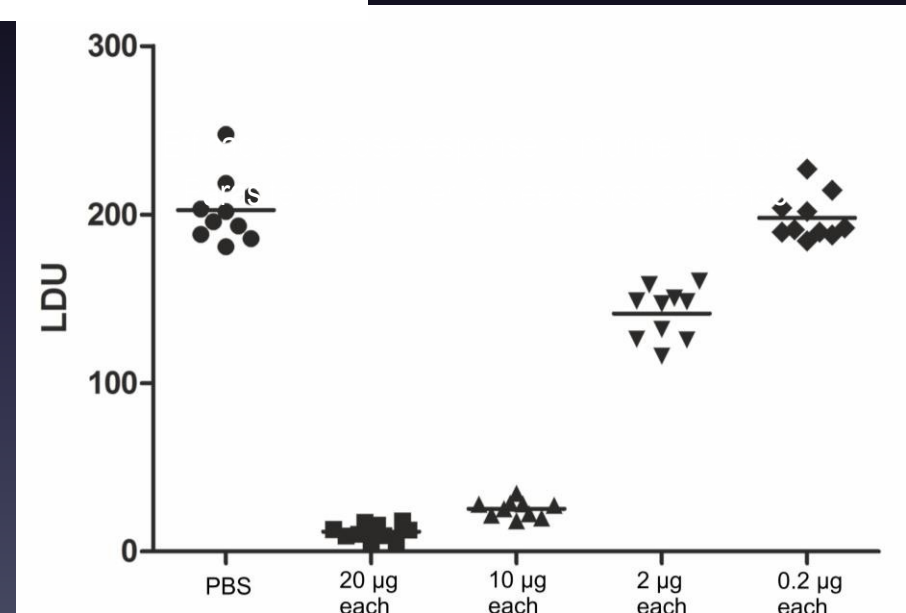
Mixture of 5 highly conserved, highly immunogenic *Leishmania* antigens encoded by small minimalistic linear DNA expression vectors



Ready to enter clinical trial:

- ✓ Preclinical efficacy and safety proven
- ✓ CD4 and CD8 T cell responses against all 5 antigens detected in target populations
- ✓ Clinical sites (VL, India & CL, Tunisia) selected, study plan outlined, clinical immunomonitoring established
- ✓ Indian pharmaceutical partner identified

GVIRF Bethesda March 2014





ORIGINAL ARTICLE

Preclinical safety and tolerability of a repeatedly administered human leishmaniasis DNA vaccine

O Riede¹, K Seifert², D Oswald¹, A Endmann¹, C Hock³, A Winkler⁴, FJ Salguero^{5,6}, M Schroff¹, SL Croft² and C Juhls¹

The leishmaniasis are a complex of vector-borne diseases caused by protozoan parasites of the genus *Leishmania*. LEISHDNAVAX is a multi-antigen, T-cell epitope-enriched DNA vaccine candidate against human leishmaniasis. The vaccine candidate has been proven immunogenic and showed prophylactic efficacy in preclinical studies. Here, we describe the safety testing of LEISHDNAVAX in naive mice and rats, complemented by the demonstration of tolerability in *Leishmania*-infected mice. Biodistribution and persistence were examined following single and repeated intradermal (i.d.) administration to rats. DNA vectors were distributed systemically but did not accumulate upon repeated injections. Although vector DNA was cleared from most other tissues within 60 days after the last injection, it persisted in skin at the site of injection and in draining lymph nodes. Evaluation of single-dose and repeated-dose toxicity of the vaccine candidate after i.d. administration to naive, non-infected mice did not reveal any safety concerns. LEISHDNAVAX was also well tolerated in *Leishmania*-infected mice. Taken together, our results substantiate a favorable safety profile of LEISHDNAVAX in both naive and infected animals and thus, support the initiation of clinical trials for both preventive and therapeutic applications of the vaccine.

Gene Therapy (2015) 22, 628–635; doi:10.1038/gt.2015.35

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Programs

GLOBAL NETWORK

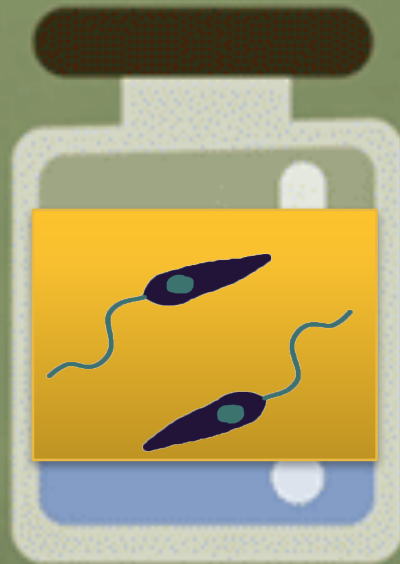
VACCINE ADVOCACY AND
EDUCATION

VACCINE DEVELOPMENT

Chagas Disease/Leishmaniasis

the Sabin Vaccine Institute in collaboration with the National Institutes of Health are investigating recombinant Leishmania antigens in combination with selected sand fly salivary gland antigens in order to augment host immunity.

LIVE ATTENUATED VACCINES



Logics:

1. The parasite once exposed people are protected for life long.
2. Leishmanization procedure in past proves it.
3. The total proteins from whole cDNA library protects better than individual subunit proteins.

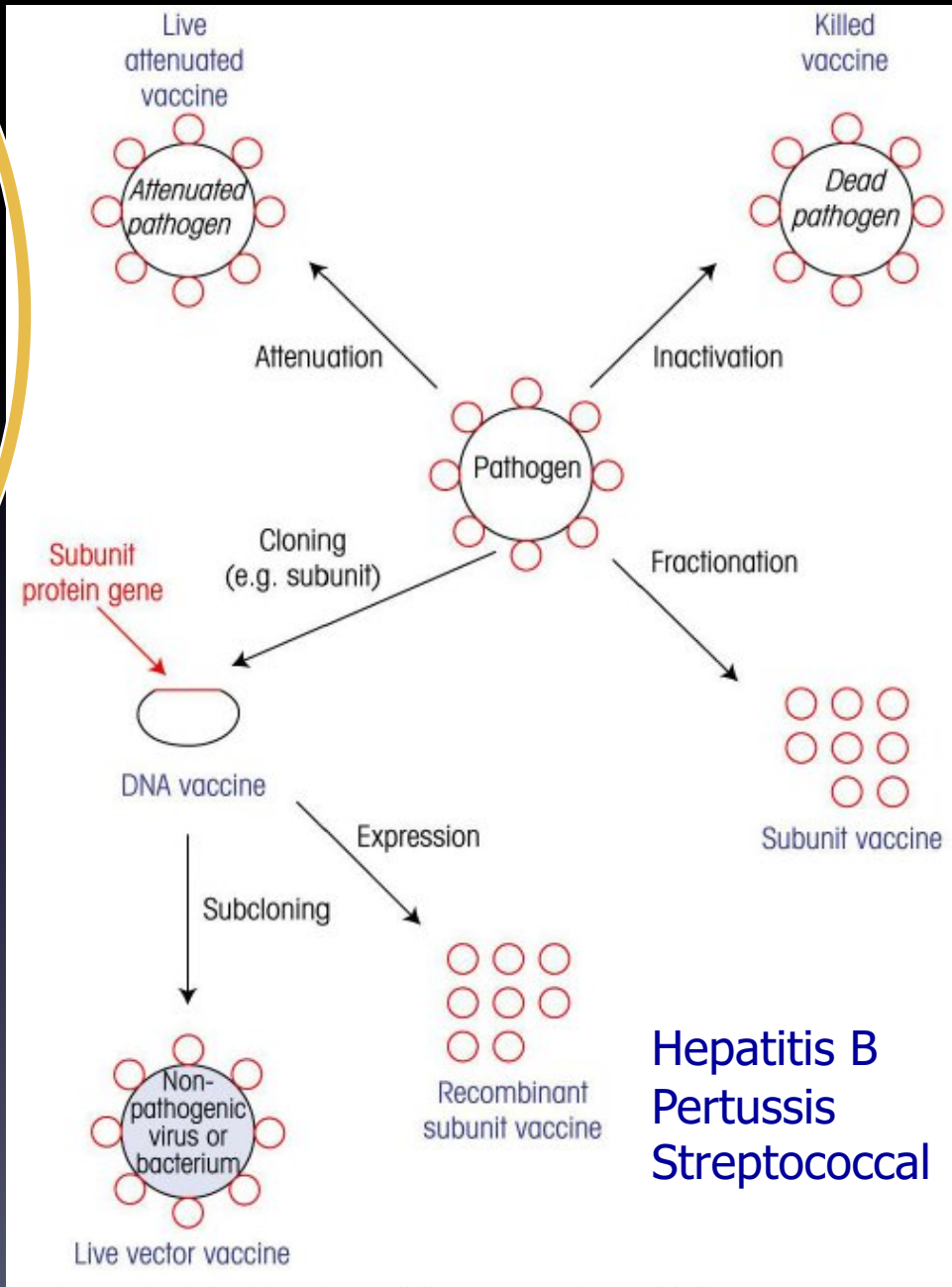
Classical Vaccine Approaches

Vaccinia virus
BCG
Measles
Mumps
Rubella
Rotavirus
Varicela
Yellow fever
Polio (sebin)
Typhoid



Many successful viral
& bacterial vaccines are
Live Attenuated vaccines

Hence try for
Leishmaniasis as well.



Cholera
Influenza
Hepatitis A
Plague
Polio (Salk)
Rabies

Diphtheria
Tetanus

Hepatitis B
Pertussis
Streptococcal

Historical Aspects of Live Vaccines

Leishmanization

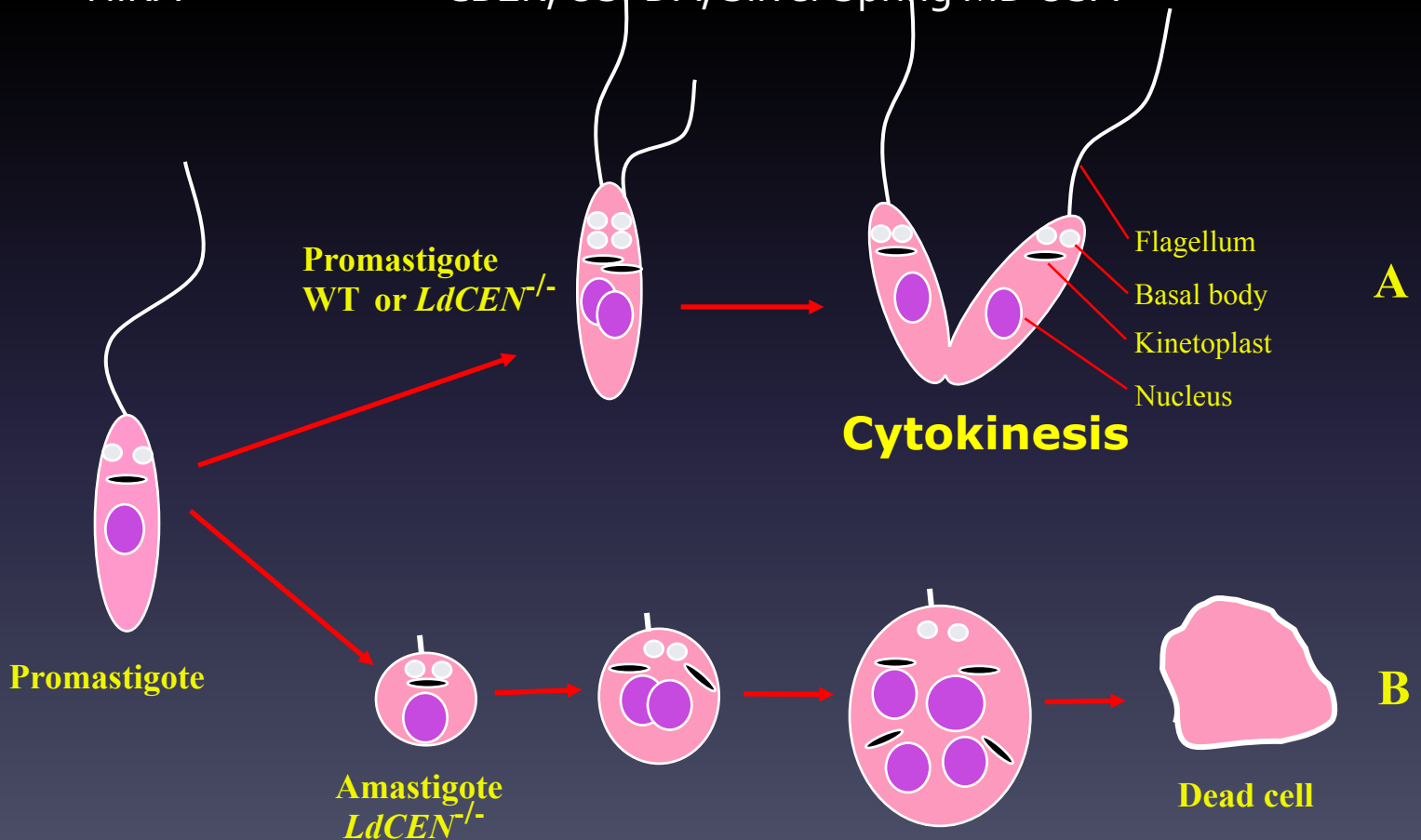
- It has been known since antiquity that individuals who had healed **cutaneous leishmaniasis** skin lesions were protected from further infections.
- Bedouin or some Kurdistani tribal societies traditionally expose their babies' bottoms to sandfly bites in order to protect them from facial lesions.
- Another ancient technique practised in the Middle East has been the use of a thorn to transfer infectious material from lesions to uninfected individuals.



Model for the stage specific impairment of cytokinesis in the absence of centrin expression in *Leishmania*

SELVA
POONAM
HIRA

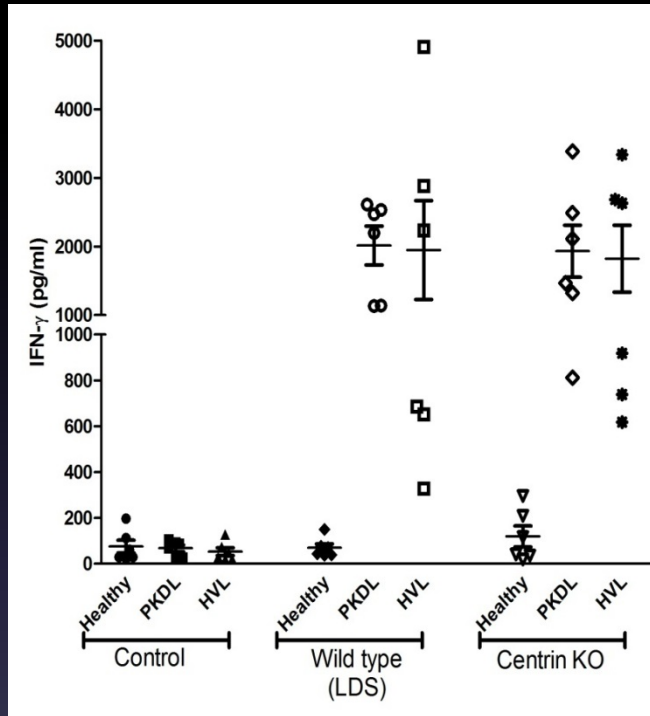
JH Institute of Molecular medicine, Jamia Hamdard New Delhi
National Institute of Pathology, New Delhi
CBER, USFDA, Silver Spring MD USA



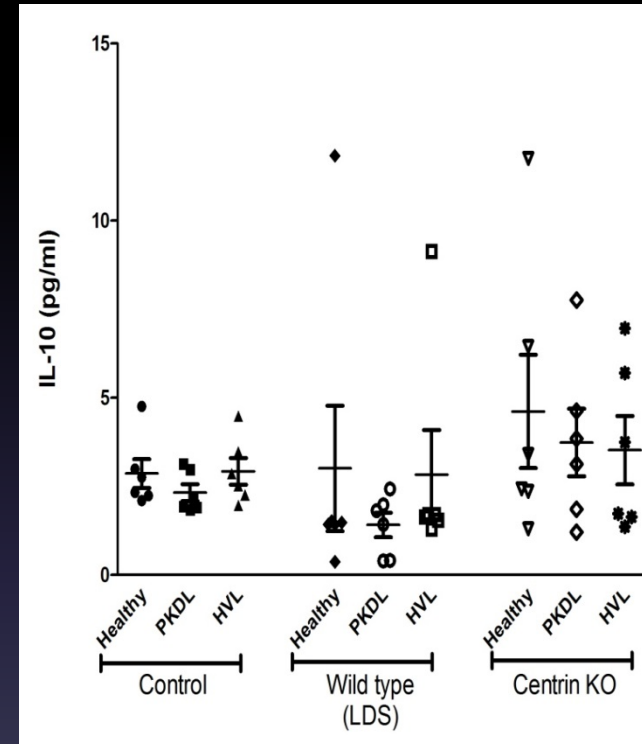
Recall Immune Response in PBMCs from PKDL and HVL patients



IFN γ



IL 10



Both HVL group and the PKDL PBMCs show significantly high IFN γ and almost unaffected IL10 cytokine expression. The ratio between these two however indicated the strong Th₁ response.

Summary: CenKO live attenuated Leishmania vaccine (Progress)

- ✓ Safe as vaccine even in immunocompromised mice,
- ✓ Protects mice, hamster and dogs against *L. donovani* with Th₁ immune response
- ✓ Cross protects against *L. braziliensis* (causes MCL) and *L. mexicana* (causes CL)
- ✓ Elicits Th₁ response in human pBMCs
- ✓ Environmentally safe since does not replicate in the sandflies
- ✓ Protection against dogs is superior to the existing canine vaccine (Leishmune^R)
- ✓ Enhanced protection in the rodents when treated with sandfly saliva proteins
- ✓ Attenuation genetic markers are identified in the parasites
- ✓ Preclinical Toxicity (at Vimta, Hyderabad) is in plan with cGLP grade material from Gennova Pharmaceuticals, Pune

Other novel vaccine approaches

The nonpathogenic to humans lizard protozoan parasite, *Leishmania (L) tarentolae*, has been attempted effectively as a vaccine platform against visceral leishmaniasis in experimental animal models

**Barbara Papadopoulou, Canada
and Sima Rafati, Iran**

Immunization with a naturally attenuated cutaneous *Leishmania donovani* isolate from Sri Lanka protects is also considered as live vaccine against visceral leishmaniasis

Greg Matlashewski, Canada

Advantages of Genetically Defined Live-attenuated Vaccines

- 1. May mimic conditions of natural infection and recovery**
- 2. Some degree of persistence without causing disease**
- 3. Timed elimination from the host**
- 4. Less chance of reversion to virulent phenotype, unless it is not a complete geneKO parasites**
- 5. Produced in large quantities in well define conditions suitable for human vaccination**
- 6. Highly cost effective.**

Disadvantages of Live-attenuated Vaccines

1. Reversion to virulent phenotype, if is not a complete geneKO parasites
2. Regulatory issues.
3. Cold chain management till the vaccinees needed.

Vaccines for leishmaniasis: Need of the hour

VL

- ❑ *Short term*: Implement available control measures
- ❑ *Long term*: Vaccine should induce Cellular and Humoral Immunity with no /minimal adverse reaction
 - An affordable field friendly safe live vaccine: Much like BCG, smallpox vaccine
 - One candidate: Live attenuated (i.e. CenKO *L. donovani*, Selvapandiyan, Salotra and Nakhasi. Better than registered vaccine for dogs.
 - Consider cost of development and implementation for all vaccines.

CL

Broad-spectrum multivalent vaccines are urgently needed, since there are no effective control measures.

Vaccine

- Protect Human Patient from infection of *L. donovani* by Sandfly bite
- Therapeutic: Prevent Asymptomatic patients from developing VL

Use infected sandfly based challenge to evaluate candidate vaccines. (must be done with caution in HIV- free foci). All participants are protected either by candidate vaccines or leishmanization.

DEVELOPMENT STATUS OF CURRENT VACCINE CANDIDATES

Candidate name/ identifier	Preclinical	Phase I	Phase II
LEISH-F2			X
LEISH-F3		X	
Various <i>Lutzomyia</i> sandfly antigens	X		
Various second generation protein based vaccines	X		
Various third generation DNA based and heterologous prime-boost vaccines	X		

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