The role of candidate vaccines in VL elimination

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**NEED FOR VACCINE?**

- Many endemic areas have not yet achieved optimal control due to logistical, biological as well as technical challenges.
- Institutional treatment regimen 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-familiar and intercommunity transmission of disease from asymptomatic cases & PKDL patients.
- Many patients do reach the caregiver in remote areas: vaccination becomes best solution.

Best way to escape..........Vaccine
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

Best way to escape .......... Vaccine
Figure. Profile of strategies used in leishmaniasis trials.

http://journals.plos.org/plosntds/article?id=info:doi/10.1371/journal.pntd.0000943
Figure . Animal models used in leishmaniasis trials.

http://journals.plos.org/plosntds/article?id=info:doi/10.1371/journal.pntd.0000943
Today there are almost 30 different characterized proteins, out of at least 8000 proteins encoded in the parasite genome, for vaccine studies.
Leishmune® 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
Vaccines such as Leish-\(F_1\), \(F_2\) and \(F_3\), developed at IDRI and designed based on selected *Leishmania* antigen epitopes, have been in clinical trials.
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 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
Preclinical safety and tolerability of a repeatedly administered human leishmaniasis DNA vaccine

The leishmaniases 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.
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.
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
Varicella
Yellow fever
Polio (sabin)
Typhoid

Cholera
Influenza
Hepatitis A
Plague
Polio (Salk)
Rabies

Many successful viral & bacterial vaccines are Live Attenuated vaccines

Hence try for Leishmaniasis as well.

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.

Adapted from Abhijit Chaudhury
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

Promastigote

WT or *LdCEN*⁻⁻/⁻

Cytokinesis

Promastigote

Amastigote *LdCEN*⁻⁻/⁻

Dead cell
Recall Immune Response in PBMCs from PKDL and HVL patients

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

Kumaravishek and Salotra et.al. unpublished
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\textsuperscript{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.

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

Barbara Papadopoulou, Canada and Sima Rafati, Iran

Greg Matlashewski, Canada
Advantages of Genetically Defined Live-attenuuated 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

- **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.

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

<table>
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<th>Candidate name/ identifier</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
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<tr>
<td>LEISH-F3</td>
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<td>Various <em>Lutzomyia</em> sandfly antigens</td>
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<td>Various second generation protein based vaccines</td>
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<tr>
<td>Various third generation DNA based and heterologous prime-boost vaccines</td>
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