Safety and immunogenicity of a new Leishmania vaccine candidate ChAd63-KH

Study Acronym: LEISH2a

ClinicalTrials.gov ID: NCT02894008

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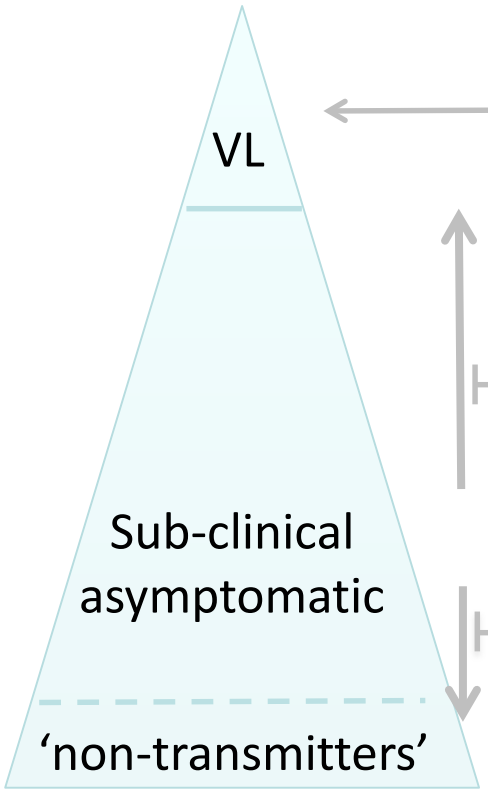
The need for a therapeutic vaccine against VL/PKDL

- Immune responses mediated diseases or spectrum:
  - Easily modulated
  - Extensive cross reactivity between parasite species
- Burden of VL/PKDL
  - Numbers of cases and deaths
  - Disfigurement
  - Transmission
- Current treatment options are far from satisfactory:
  - Toxic
  - Expensive
  - Logistics
  - emerging resistance
  - co-infections on increase
- Previous therapeutic vaccines experience showed promise:
  - PKDL in Sudan

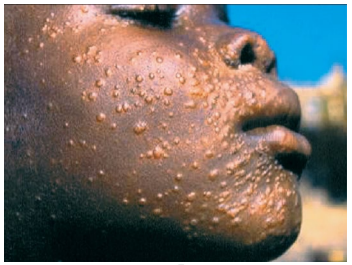
Targets for therapeutic vaccination in visceral leishmaniasis / PKDL

Visceral leishmaniasis → PKDL



Can we improve treatment for patients

dose sparing, reduced drug failure / relapse / PKDL



Can we prevent development of clinical disease?

improved quality of life

Can we stop PKDL patients from transmitting?

Can we stop asymptomatic patients from transmitting?

reduced community level transmission and quality of life

Immunochemotherapy of PKDL

- **Objectives:**

- To develop an affordable protocol of treatment.
- To shorten treatment duration.
- To reduce cost of treatment by 50%.
- Less exposure to toxic drugs.

Rationale for a therapeutic $CD8^+$ T cell-inducing vaccine against leishmaniasis

- $CD8^+$ T cells are the major correlate of protection.
- Increased activated $CD8^+$ T cells asymptomatic and treated VL patients.
- therapeutic vaccination in experimental models of VL, dependent upon induction of $CD8^+$ T cells.
- effector memory $CD8^+$ T cells can be re-activated in mice with ongoing VL, leading to reduced parasite burden.
- the pathology associated with established experimental VL is similar to that observed in human disease.

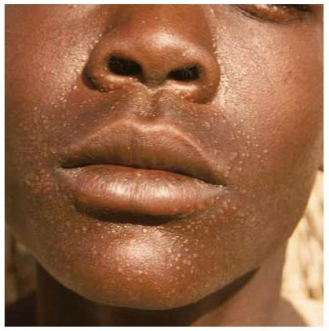
Collectively, both priming of naïve $CD8^+$ T cells and the activation of pre-existing effector/memory $CD8^+$ T cell responses can occur in the face of disease-associated pathology.

Human Anti-leishmania Vaccine Studies

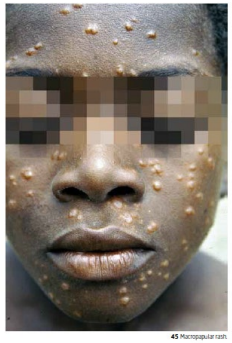
- No effective vaccine has yet been developed for VL / PKDL despite significant research efforts.
- $CD4^+$ T cells targeted candidate vaccines need revision.
- based on the importance of $CD8^+$ T cells for protection against leishmaniasis, we have sought to develop a novel therapeutic vaccine for VL / PKDL, biased towards the induction of $CD8^+$ T cell responses.

ChAd63-KH: Vaccine clinical development

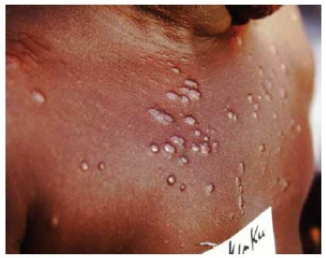
Dooka, Gedaref State,
Eastern Sudan



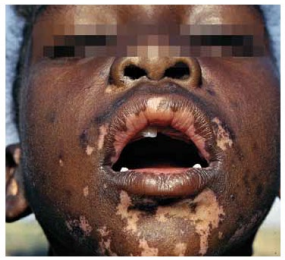
44 Micropapular rash.



45 Micropapular rash



66 Nodular lesions.



- Valuable clinical target (individual and community benefit)
- No animal models
- Chronic but non-life threatening
- High case rate, including persistent disease
- Good clinical endpoints defining cure
- Experienced clinical site
- Good regulatory environment

ChAd63-KH

chimpanzee Adenovirus 63- KH

(KH: Kinteoplastid Membrane Protein 11 + Hydrophilic Acylated Surface Protein B

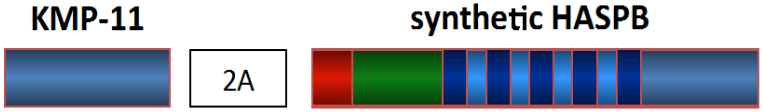
KMP-11 + HASPB

- ChAd63-KH is a replication defective simian adenovirus
- expressing a novel synthetic gene (KH) encoding two *Leishmania proteins KMP-11 and HASPB.*
- $CD8^+$ T cells-based candidate vaccine.
- has been developed at the University of York by Prof Paul Kaye and his team.
- The vaccine has already been shown to be safe, well tolerated and able to induce a good immune response in healthy subjects.
- is currently in a further safety study in PKDL patients.

Therapeutic CD8+ T cell-biased vaccines for human VL/PKDL

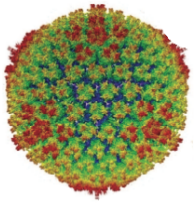
Program PI: Paul Kaye

The insert….



Engineered to reflect strain diversity in SE Asia/E. Africa

The viral vector….



ChAd63

- produced in suspension culture Procell 92 cell line for scalable manufacture
- Safety and immunogenicity data available from hundreds of volunteers

Preclinical proof of concept….

The Journal of Infectious Diseases

- Maroof et.al. *JID.* 2012. **205**:853–63

The clinical trial….

LEISH1: A study to assess the safety and immunogenicity of a new Leishmania vaccine candidate ChAd63-KH

ISRCTN ISRCTN07766359

Phase Isfirt -in-human study: dose escalating, "prime only"

- Excellent safety profile confirmed
- Excellent levels of CD8+ T cell responses (breadth / magnitude / % responders)

UNIVERSITY of York · HYMS THE HULL YORK MEDICAL SCHOOL · okairos from genes to vaccines · ROBERT KOCH INSTITUT · wellcome trust

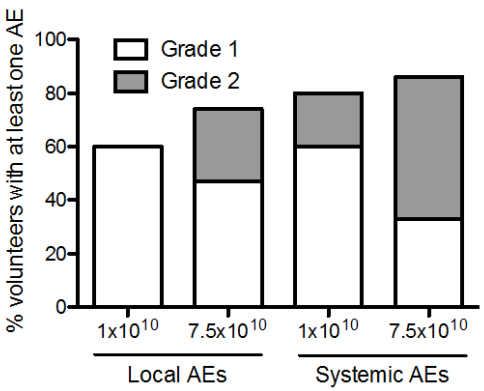
LEISH1: A first-in-human clinical trial of ChAd63-KH

Trial design: dose escalation, open label; healthy UK adults

RESEARCH ARTICLE PLOS | NEGLECTED TROPICAL DISEASES

A third generation vaccine for human visceral leishmaniasis and post kala azar dermal leishmaniasis: First-in-human trial of ChAd63-KH

Safety



Injection site redness, swelling, pain, headache and tiredness, transient lymphopenia: **safety profile similar to other adeno-viral vectored vaccines**

$CD8^+$ IFNɣ ELISpot

$CD8^+$ Flow cytometry

Robust $CD8^+$ T cell response 100% (20/20) responders: ***single dose administration is immunogenic in healthy volunteers***

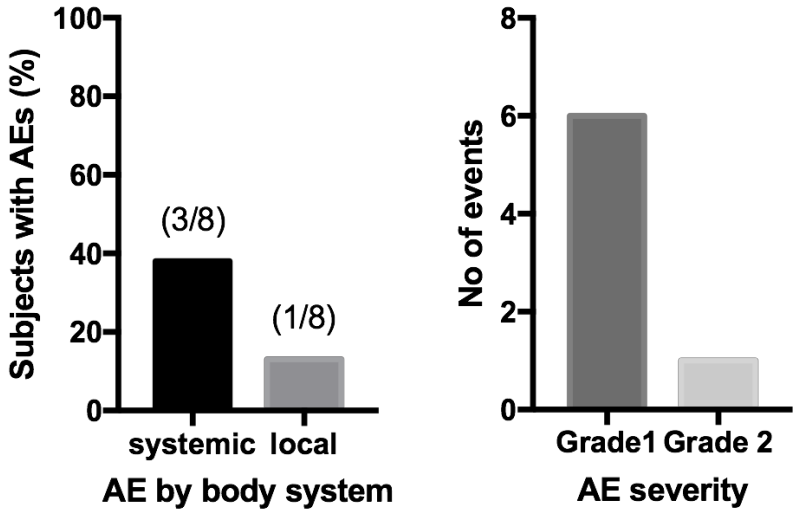
Osman et al *PLoS Neglect. Trop. Dis.* 2017. 11(5):e0005527.

Leish2a: Preliminary results

Phase IIa, open label dose escalation, age de-escalation study in 24 patients with persistent PKDL:

- Well -tolerated with no grade 3 or 4 reactions.
- Immunogenicity ($CD8^+$ T cell IFNɣ ELISpot) on par with healthy UK adults
- Final arm to be completed Dec 2018

LEISH2a: Low dose adult cohort safety data



N=8: Adults (18-50); $1x10^{10}$ vp i.m.

DSMB recommendation to proceed to dose escalation: Feb 2017

High dose completed April 2018 and awaiting DSMB review before age de-escalation

Preliminary immunogenicity data suggests responses on par with healthy UK volunteers

First patient vaccinated with ChAd63-KH

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okairos
from genes to vaccines

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….and our trial volunteers