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

Study Acronym: LEISH2a
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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

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 asymptomatic patients from transmitting?
- reduced community level transmission and quality of life

Can we stop PKDL patients from transmitting?
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

- 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

Dooka, Gedaref State,
Eastern Sudan
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

**The insert....**

- KMP-11
- synthetic HASPB

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 clinical trial....**

- Phase I trial - in-human study: dose escalating, “prime only”
  - Excellent safety profile confirmed
  - Excellent levels of CD8+ T cell responses (breadth / magnitude / % responders)

[Logos and mentions of institutions and organizations]
LEISH1: A first-in-human clinical trial of ChAd63-KH

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

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

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

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 IFNγ 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); $1\times10^{10}$ 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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....and our trial volunteers