



# Vaccine candidates and their selection for phase 2/3 trials based on phase I immunological data

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Disclosure: The presenter is a co-inventor on patents related to prime-boost immunisation



# Accelerated Monovalent Ebola Vaccine Development

- Chimpanzee adenovirus 3 vaccine (“cAd3-EBO”)
  - Monovalent Zaire strain
  - Previously used for hepatitis C phase I/II trials
- WHO / Oxford / Wellcome / GSK / Okairos / NIH plan
  - Phase I in Oxford mid-September: 60 vaccinees
  - Phase I in Mali: 91 vaccinees
  - Phase I in Lausanne: 100 vaccinees
  - Phase I at NIH / Maryland: >20 vaccinees
- Objectives by end December 2014
  - Safety data in >250 volunteers, especially healthcare workers
  - Immunogenicity comparable to protected macaques



# Oxford Ebola Vaccine Trial



- First ChAd3 EBOZ vaccination 17 September 2014
- Three dose levels assessed in 60 vaccinees
  - $1 \times 10^{10}$  vp,  $2.5 \times 10^{10}$  vp,  $5 \times 10^{10}$  vp (n = 20 each)
  - Approval to immunise in West Africa given by Data Safety Monitoring Board by 4 October 2014



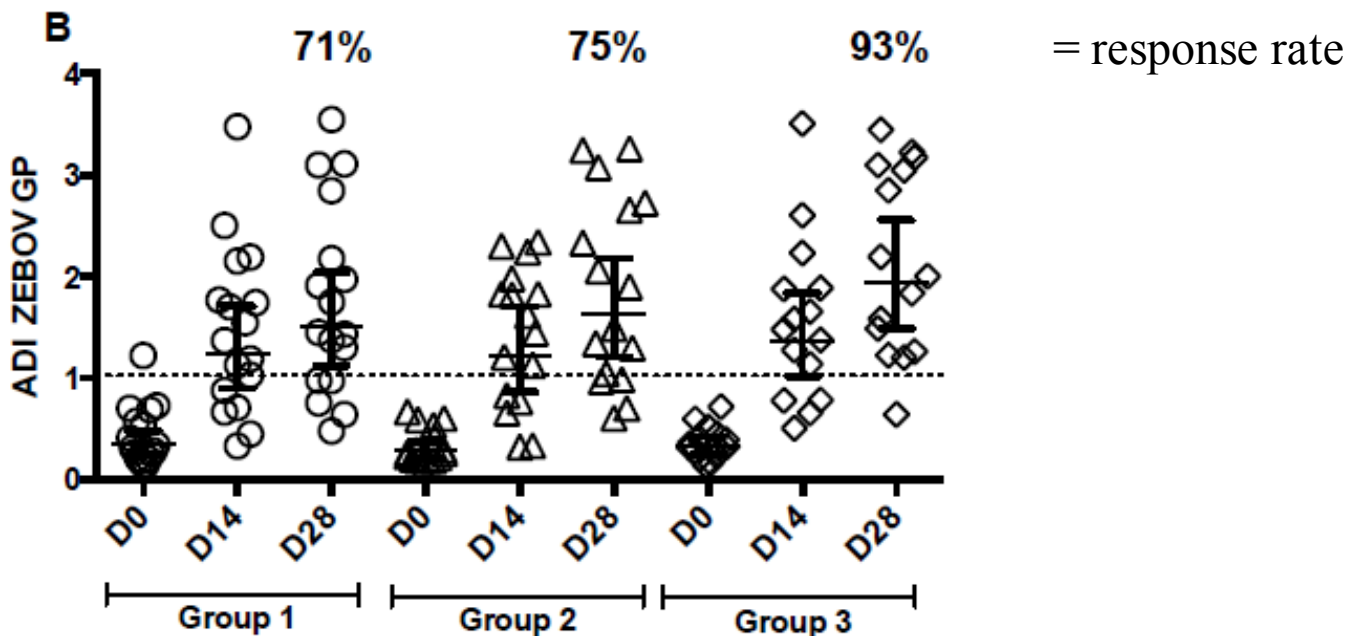
# Trial Timeline

14 August	Grant submitted
26 August	Award letter
8 September	Ethical approval
9 September	Regulatory approval
17 September	1 <sup>st</sup> ChAd3 vaccinee
4 October	Mali trial approval
18 November	60 <sup>th</sup> ChAd3 vaccinee
26 November	1 <sup>st</sup> MVA vaccinee
9 December	30 <sup>th</sup> MVA vaccinee



# EBOZ Antibody Immunogenicity

## ADI ELISA



ADI (Alpha Diagnostics International) assay correlation with NIH assay:  $r = .92$ ,  $p < 0.0001$



# Comparison with NIH trial of bivalent vaccine

ChAd3 EBO Zaire + Sudan  
 $2 \times 10^{10}$  or  $2 \times 10^{11}$  vp, single dose

GMT 331 or 2037 four weeks after immunisation, in NIH assay against Ebola Zaire Mayinga

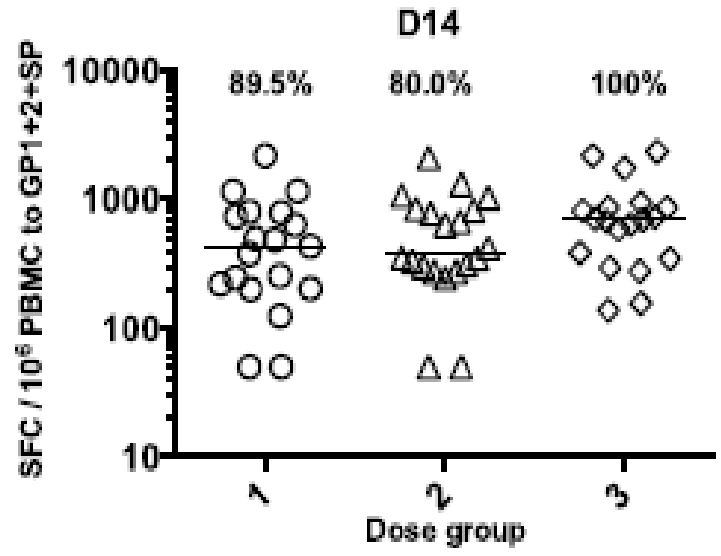
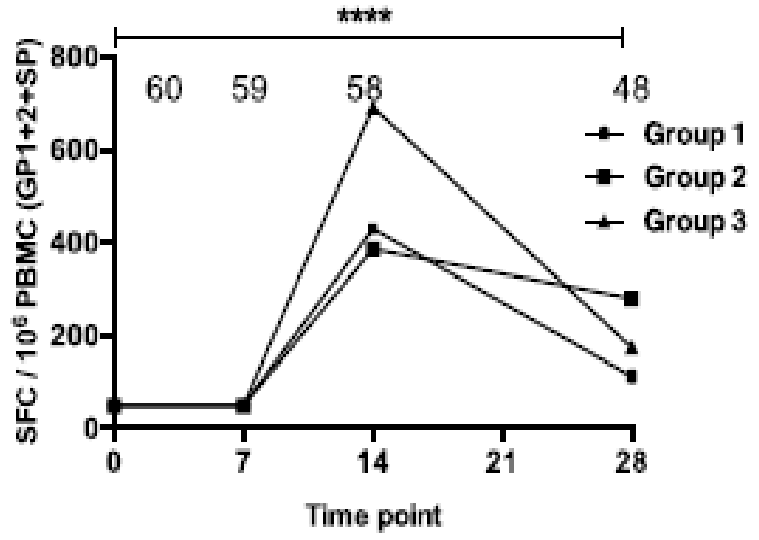
In the Oxford trial the GMT was 575 in the high dose group (same assay, same timepoint, data from 20 subjects)

In macaques the correlate of protection was 3700

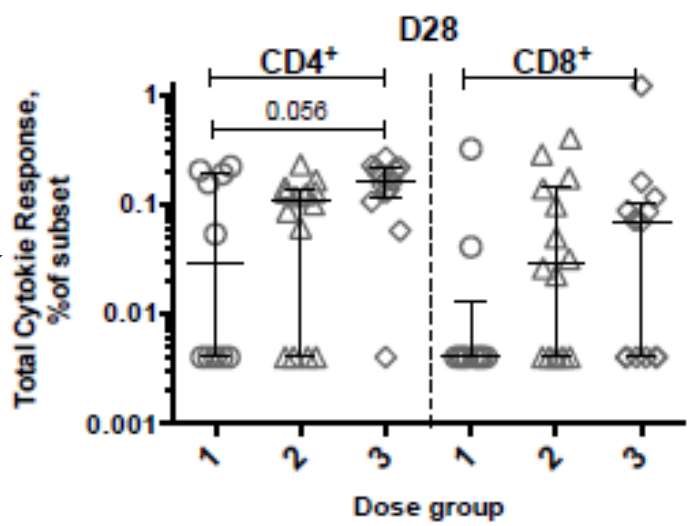


# T Cell Immunogenicity

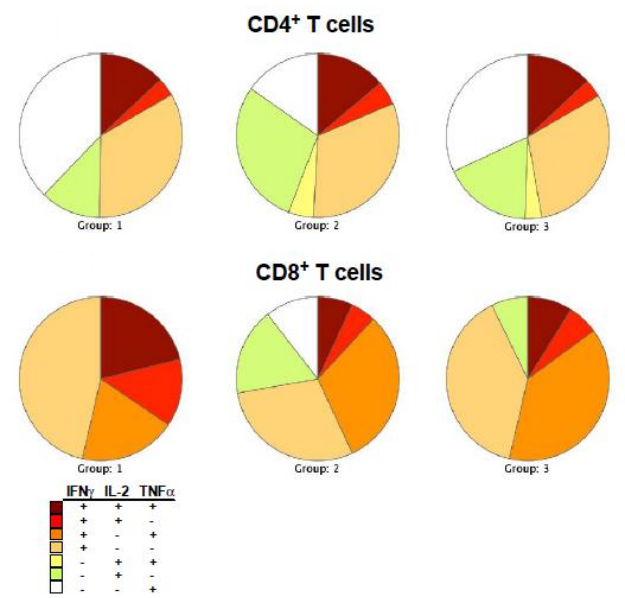
ELISpot



Flow Cytometry



0.07% mean





# **Modified Virus Ankara (MVA)**

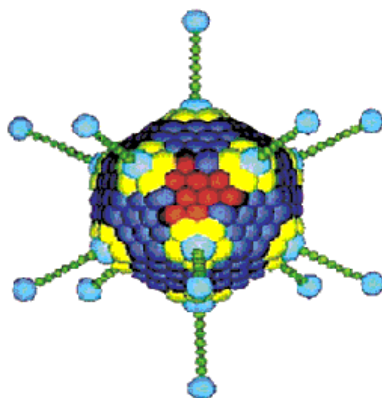
## **The Leading Booster Vaccine**

- **120,000 MVA vaccinees during 1970s**
- **First clinical trial of recombinant MVA boosting: 1999**
- **Since then over 115 clinical trials as a booster**
  - 50 for malaria (9 inserts), 35 for TB, 20 in HIV, 5 in influenza, 4 for HCV, 1 for RSV: at least 20 inserts
  - >1000 vaccinees in malaria, >2000 in TB, >1000 others
  - Therapy: >600 cancer patients; > 100 HIV, HCV patients
- **>5000 subjects immunised with recombinant MVAs**



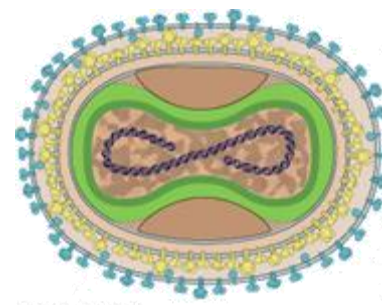


# Viral Vector Vaccines to Maximise Cellular Immunogenicity



**Adenovirus Prime**

8 weeks



**MVA Boost**

Malaria, HCV, HIV, influenza, TB, RSV, Ebola





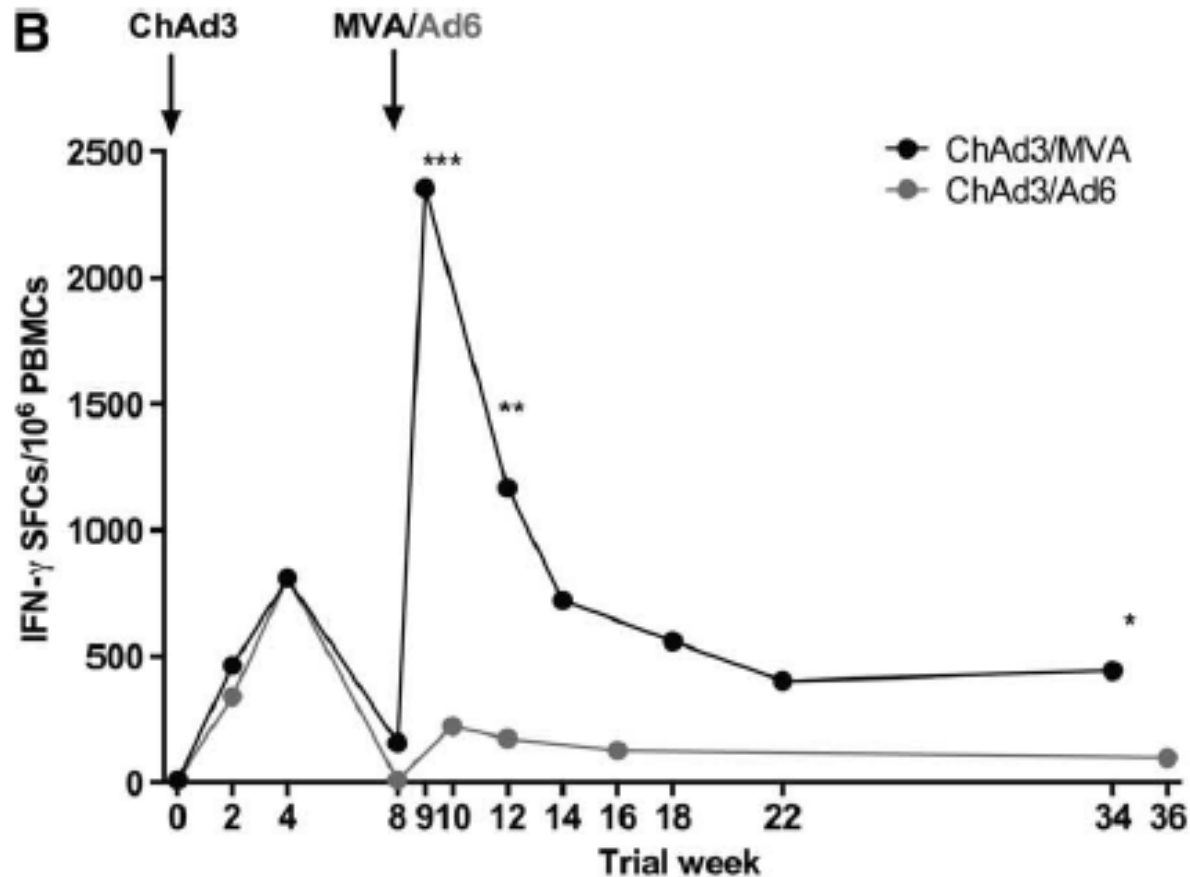
# ChAd-MVA Trials

**30 trials for 7 disease area**

- From December 2007
  - 20 malaria trials: all ChAd63-MVA
    - **7 in Africa: adults, children, infants (650 vaccinees)**
  - 4 HCV trials: all ChAd3 prime MVA NS<sub>mut</sub> boost
  - 1 HIV trial: ChAd63- MVA HIVconsv
  - 1 Influenza: ChAdOx1-MVA NP+M1
  - 2 Tuberculosis: ChAdOx1-MVA Ag85A
  - 1 RSV: PanAd3-MVA
  - 1 Ebola: ChAd3-MVA (Ad26-MVA from late December 2014)
- Over 1500 vaccinees to date



# HCV Responses with Prime-Boost Regimes: ChAd3-MVA more immunogenic than ChAd3-Ad6





# Malaria ME-TRAP T Cell Immunogenicity in the Clinic

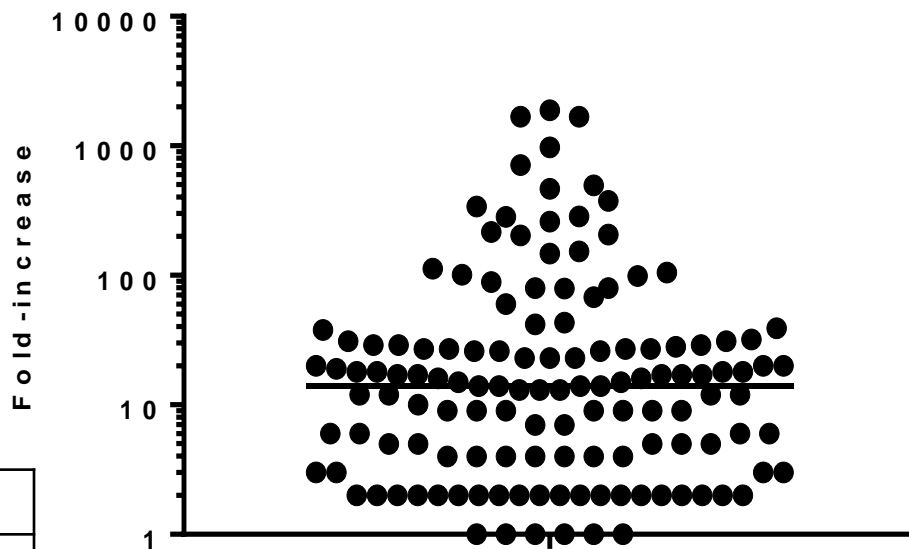
<b>VACCINE</b>	<b>T CELL RESPONSE</b> mean cells/ million PBMCs	<b>ANTIGEN</b>
DNA x 3	48	ME-TRAP
Fowlpox x 2	50	ME-TRAP
MVA x 3	41	ME-TRAP
<b>ChAd63 x 1</b>	<b>850</b>	<b>ME-TRAP</b>
DNA x 2 - MVA	430	ME-TRAP
Fowlpox x 2 - MVA	475	ME-TRAP
<b>ChAd63-MVA</b>	<b>2800</b>	<b>ME-TRAP</b>

**0% sterile efficacy with ChAd alone; 21% - 67% with ChAd - MVA**



# TRAP Antibody Titres Boost 14-fold after MVA (n=132 subjects)

Overall Fold-Increase in Anti-TRAP Antibody Titre after MVA Boost n=132  
volunteers



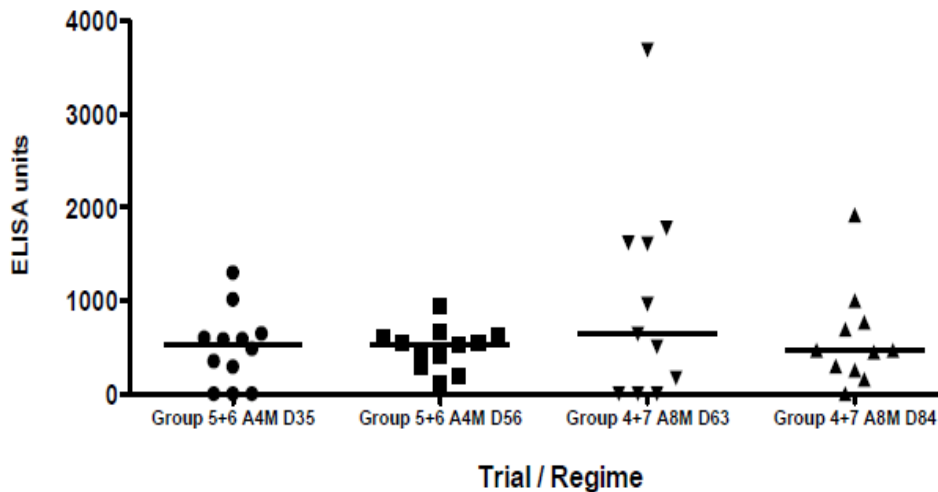
Minimum	1
25% Percentile	4
<b>Median</b>	<b>14</b>
75% Percentile	31
Maximum	1879

Georgina Bowyer  
et al. unpublished



# No impact on TRAP Ab titres of reducing 8 week to 4 week ChAd-MVA interval

4 Week vs 8 Week Prime

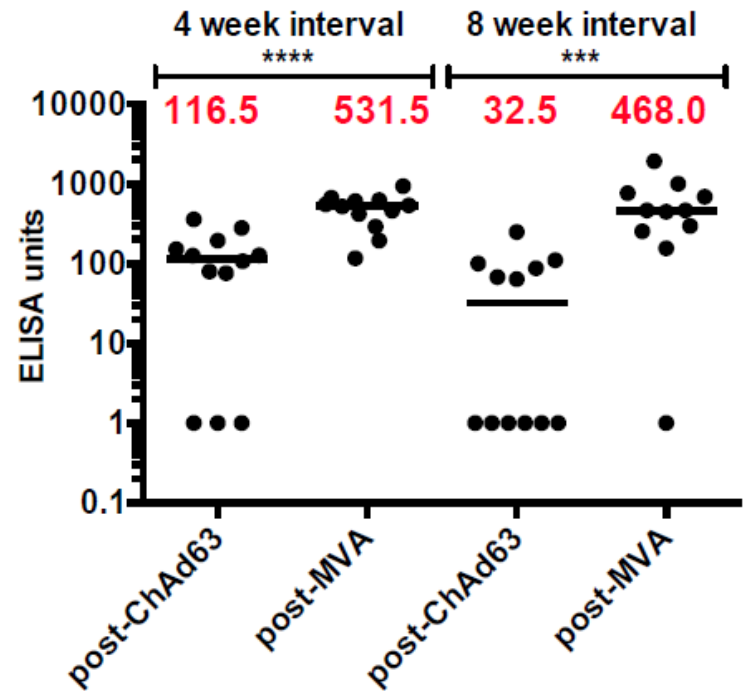


No significant difference between A4M prime and A8M prime.

Kruskal-Wallis test: P value=0.8682

Mann Whitney test (D35 vs D63): P value=0.3847

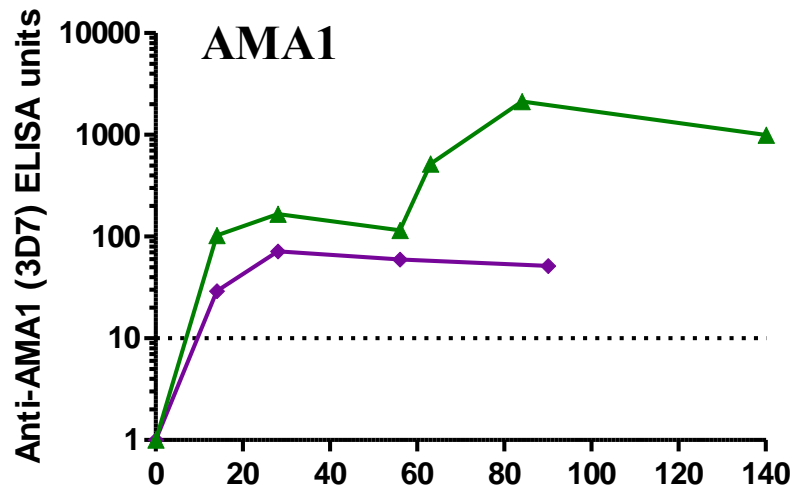
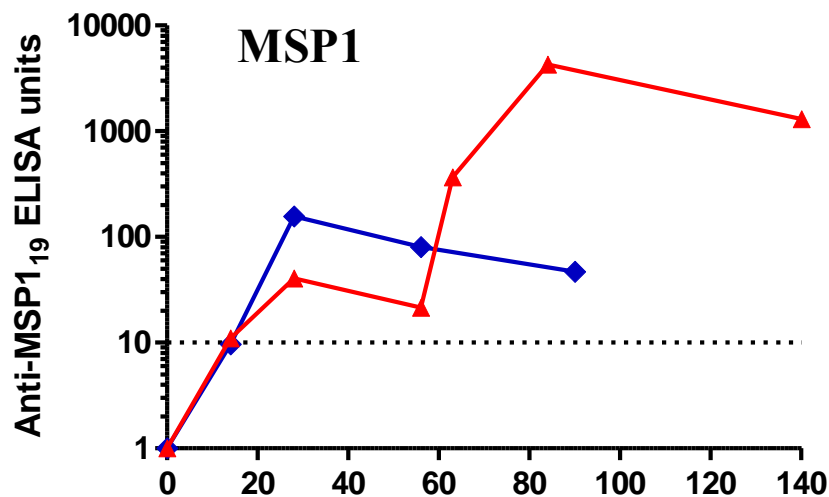
Mann Whitney test (D56 vs D84): P value=0.9754





# MVA Boosts MSP1 & AMA1 Antibodies

ChAd63-MVA Phase Ia malaria clinical trials



ChAd63 prime =  $5 \times 10^{10}$  vp (i.m.)    MVA boost =  $1.25 - 5 \times 10^8$  pfu (i.m.)

Ab Boost Post-MVA: **MSP1: 35-fold**    **AMA1: 30-fold**



# Two MVA Products Availability

- MVA-BN Filo
  - Used in Oxford trial
  - Glycoproteins of Zaire and Sudan strain of Ebolavirus
  - and nucleoprotein of Tai Forest strain of Ebolavirus
  - and Marburg virus glycoprotein
  - Large scale manufacture at Bavarian Nordic in progress
- MVA-EBOZ (GSK)
  - NIH doses manufactured
  - Large scale manufacture at Emergent Biosolutions underway





# MVA EBO Boost Design

- 30 of the total of 60 ChAd3 EBOZ vaccinees boosted with MVA BN Filo
  - at 3 – 10 weeks (mean of 6 weeks)
  - 10 subjects from each ChAd3 dose level
  - Dose either  $1.5 \times 10^8$  or  $3 \times 10^8$  pfu
- MVA was well tolerated



# New trial commencing in Oxford

- A Phase 1, First-in-Human Study to Evaluate the Safety, Tolerability and Immunogenicity of Heterologous Prime-Boost Regimens Using MVA-BN-Filo and Ad26.ZEBOV Administered in Different Sequences and Schedules in Healthy Adults
- PI Matthew Snape, Sponsor Crucell (Johnson & Johnson)
- Prime boost study using
  - $5 \times 10^{10}$  vp Ad26 ZEBOV GP
  - $1 \times 10^8$  TCID<sub>50</sub> MVA-BN-FILO
- Four groups, plus placebo control group
  - Ad26/MVA or MVA/Ad26
  - Four or eight week interval
- 72 volunteers in total, started December 2104.



# Summary

- ChAd3 EBOZ in 60 Oxford vaccinees
  - was well-tolerated and immunogenic
  - but antibodies and T cells were x10 and x5 lower than levels in protected macaques
- Heterologous boosting with MVA
  - was well tolerated
  - boosted T cell and antibodies substantially
- These data support evaluation of both ChAd3 alone and ChAd3-MVA in efficacy trials



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