



Bringing innovation to global health

Development of AERAS-402/Crucell Ad35.TB Vaccine

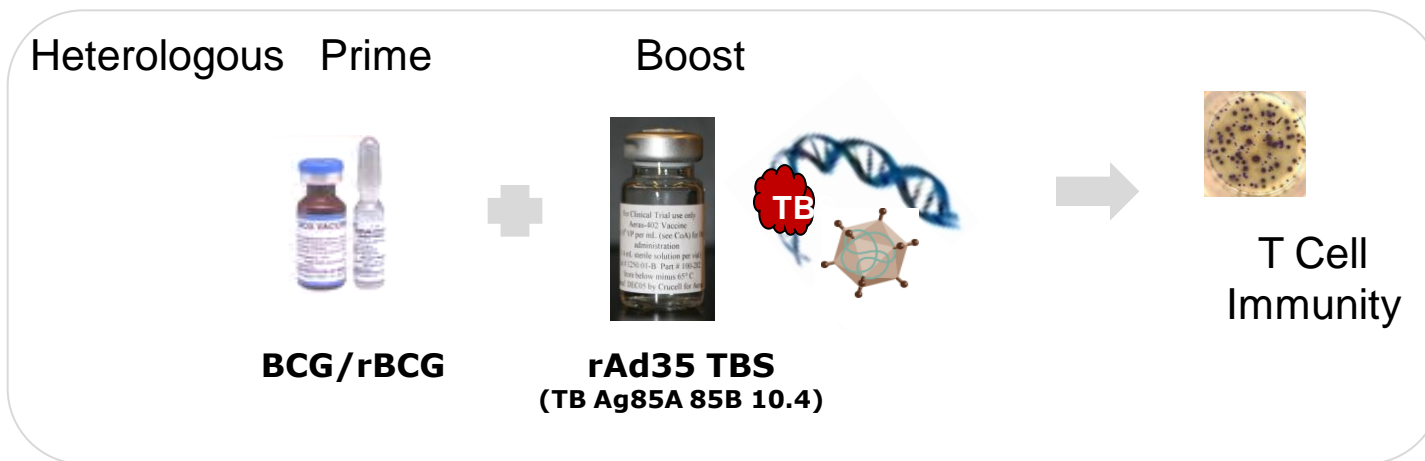
The Second Global Forum on TB Vaccines
Tallinn, Estonia
September 21-24 2010

Jerald Sadoff,
Chief Medical Officer



Aim of Crucell/AERAS TB vaccine program

- Development of an rAd35 AdVac[®] vaccine for prophylaxis against TB, as boost to BCG, widely available and affordable in endemic countries



Tuberculosis Program

GOAL

- Development of a rAd35 AdVac[®] vaccine for prophylaxis against TB, as boost to BCG or rBCG

PRODUCT

- rAd35 delivering 3 MTb Ag's as a single fusion protein: Ad35.TBS (Aeras-402)
- Two intramuscular doses of Ad35.TBS following BCG or rBCG

STATUS

- Safety and immunogenic response demonstrated in different risk strata
- Phase II in HIV⁺ adults started in 2010
- Phase II in infants, dose finding to start in 2010

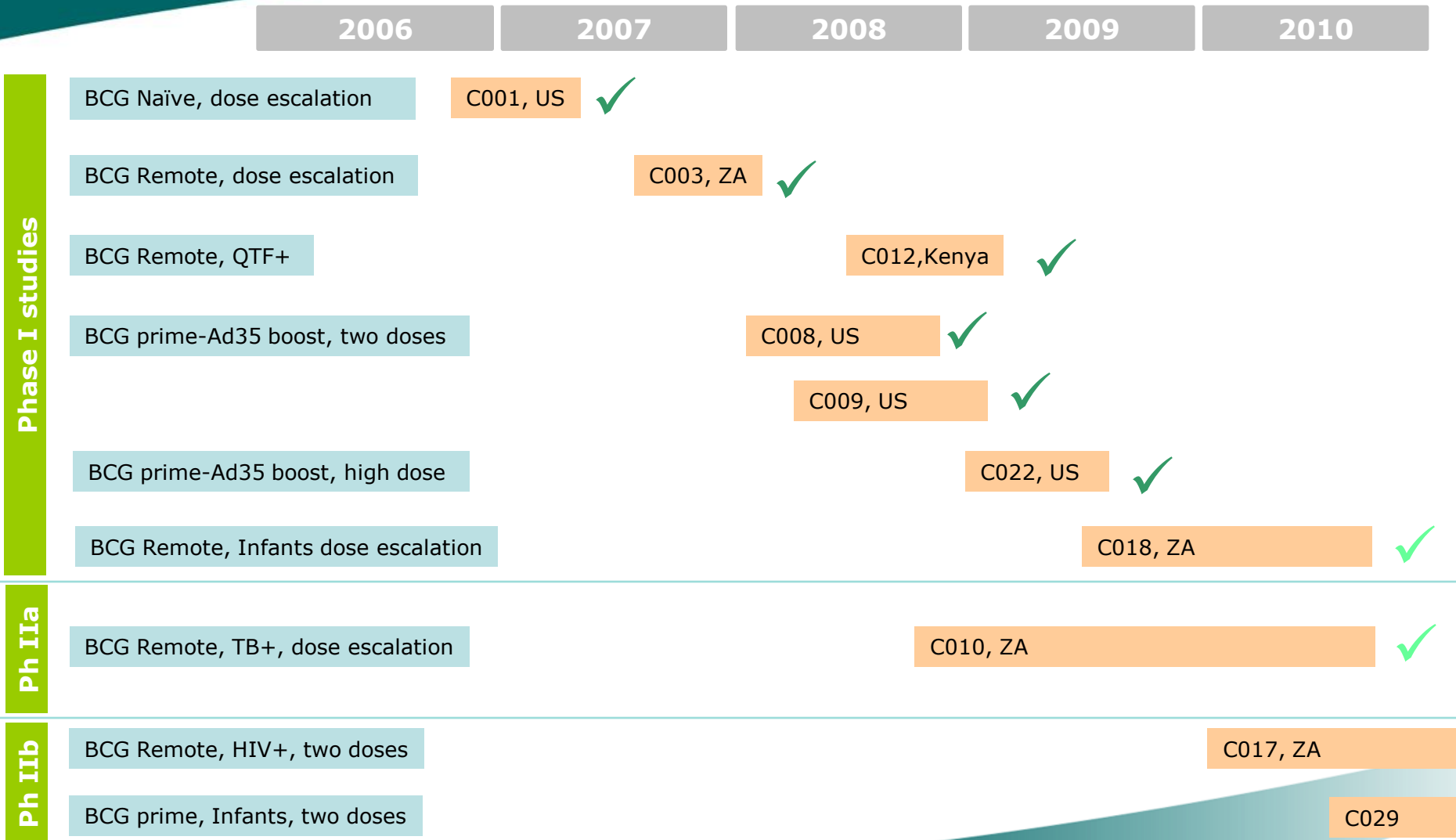
PARTNER

- Aeras

Summary Clinical studies

2006-2010

✓ completed ✓ fully enrolled



Summary Clinical studies

2006-2010

Safety in adults

- Over 150 adults received Ad35.TBS so far
- Data demonstrate an acceptable safety profile of Ad35.TBS at all dose levels evaluated

Immunogenicity in adults

- Ad35.TBS improves BCG-primed immune response enhancing antigen specific T cell responses
 - Ad35.TBS induces predominantly CD8 T cells expressing IFN- γ and/or TNF- α
 - Ad35.TBS capable to stimulate CD4 T cell responses dominated by a polyfunctional population co-expressing IFN- γ , TNF- α , and IL-2 (*B. Abel et al, AJRCCM 2010*)

Safety in infants

- Over 40 infants received Ad35.TBS so far
- Available Phase I data demonstrate an acceptable safety profile

Immunogenicity in infants

- Predominantly CD8+ T-cell responses observed in the high dose group

BCG-Ad35.TBS Prime Boost Trial (C-008-402)

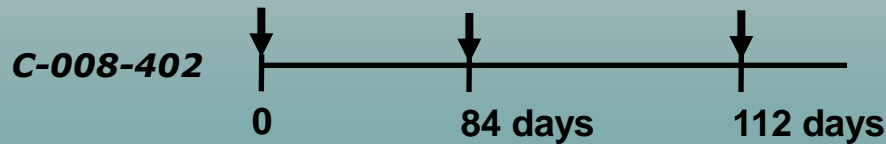
Randomized, double-blind, placebo-controlled phase I study

Clinical site: *St. Louis University Center for Vaccine Development*

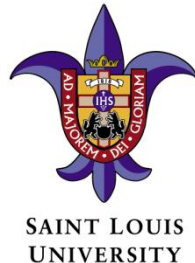
All volunteers were BCG naive



- Primary endpoint:
 - Adverse events
- Secondary endpoint:
 - Immunogenicity

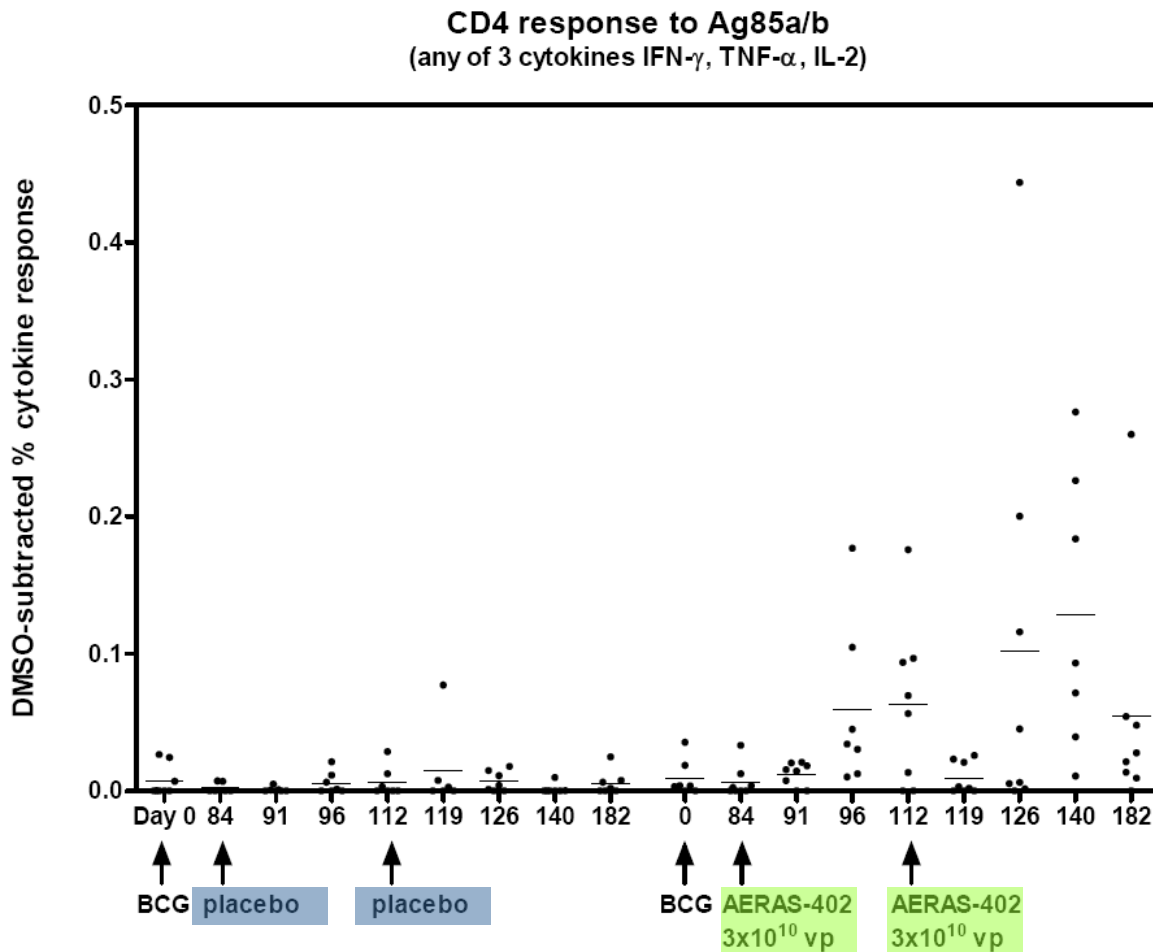


Study completed;
tables & listings received



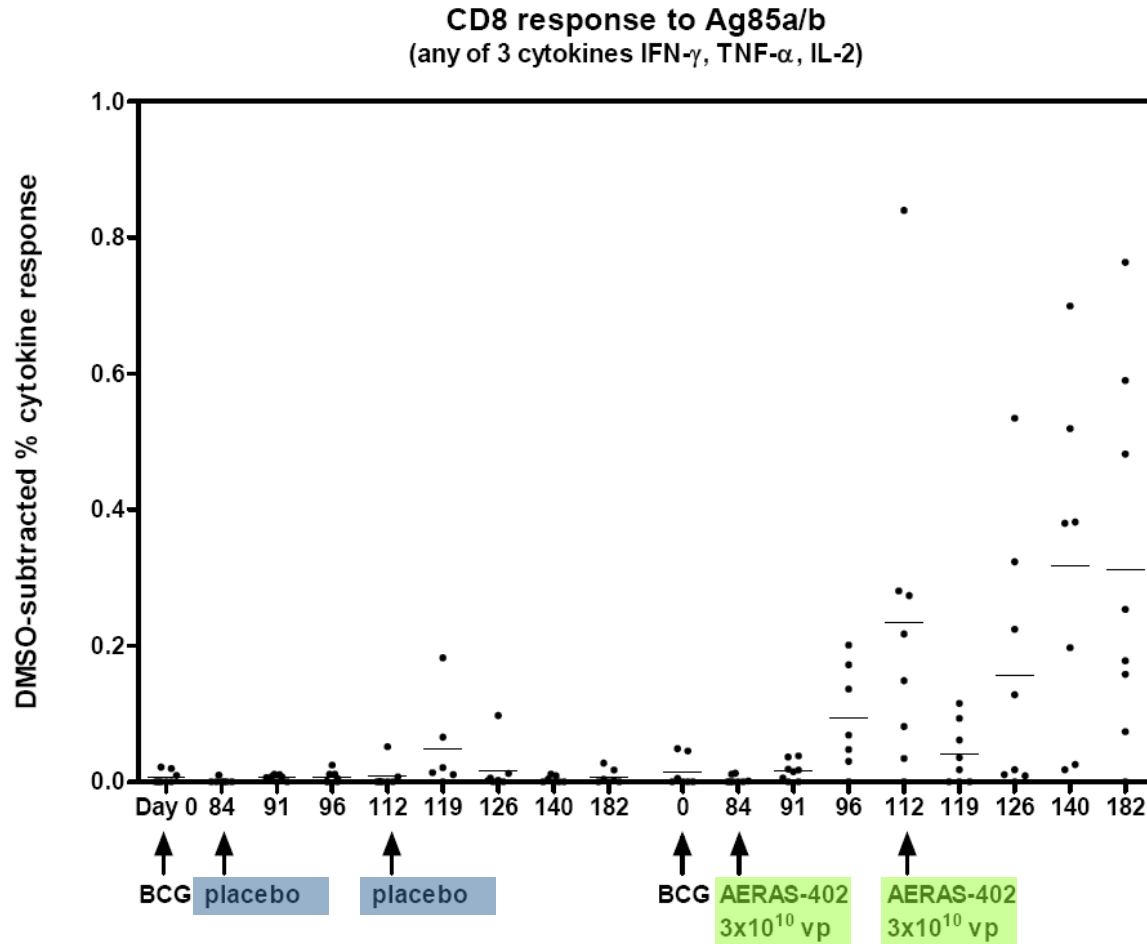
BCG-Ad35.TBS Prime Boost Trial (C-008-402)

CD4+ responses to Ag85a/b by ICS



BCG-Ad35.TBS Prime Boost Trial (C-008-402)

CD8+ responses to Ag85a/b by ICS



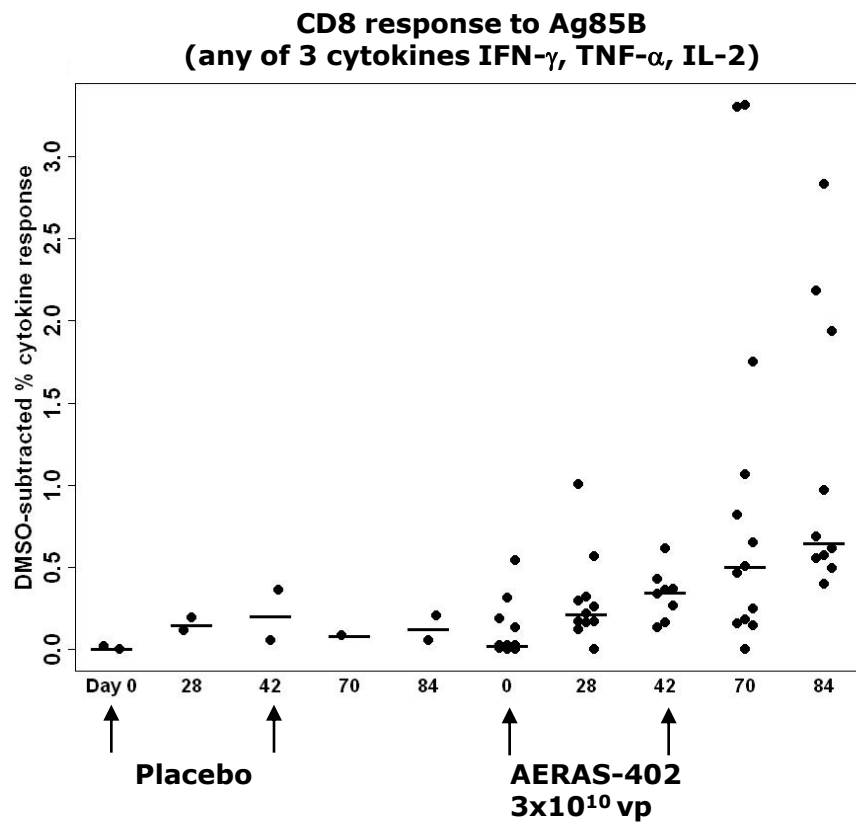
Results:

- 2 doses induce high levels of CD8+ T-cell responses
- CD4+ T-cell responses are measurable, but less prominent

Phase II trial in adults treated for pulmonary TB (C-010-402)

CD8+ responses to Ag85B by ICS

Tuberculosis patients 1-4 months on treatment



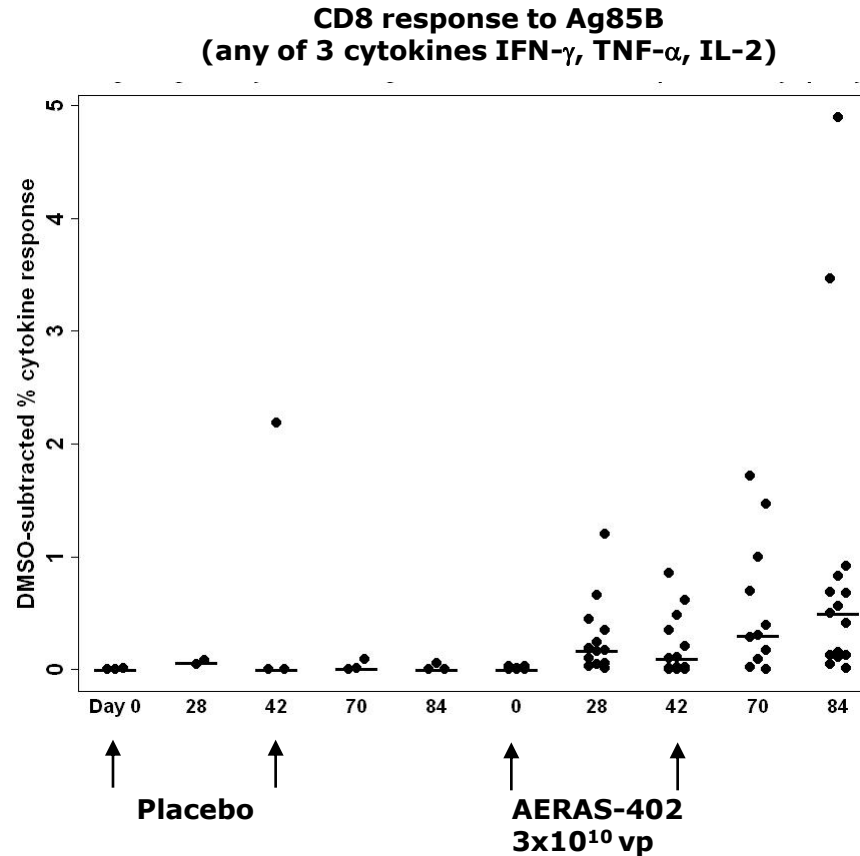
AERASSM
GLOBAL TB VACCINE FOUNDATION



See Poster Nr. 37, S. Bennet et al

Phase II trial in adults treated for pulmonary TB (C-010-402) CD8+ responses to Ag85B by ICS

Tuberculosis patients 12+ after start of treatment



See Poster Nr. 37, S. Bennet et al

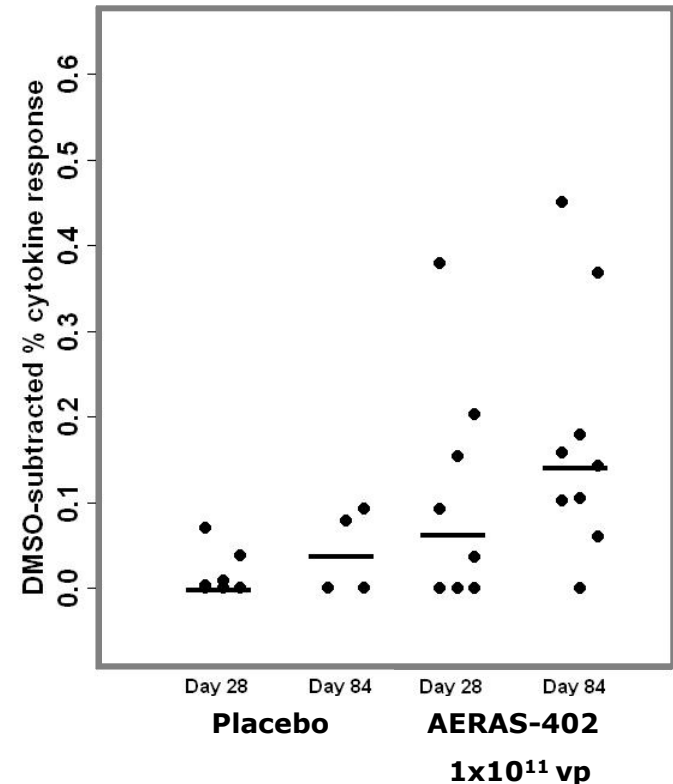
Phase I study in infants (C-018-402)

Preliminary data- CD8+ responses to Ag85B by ICS



Healthy infants aged 6-9 months were vaccinated at day 0 and day 56

CD8 response to Ag85B
(any of 3 cytokines IFN- γ , TNF- α , IL-2)



Phase IIb Proof of Concept Study in Infants

- Study C-029-402: Phase II, Double-blind, Randomized, Placebo-controlled, Multicenter, Proof-of-concept Study of Ad35.TBS/AERAS-402 in BCG-vaccinated, HIV-uninfected Infants Without Evidence of Tuberculosis (age =16-26 weeks)
- Primary Objectives
 - To evaluate the safety profile of Ad35.TBS/AERAS-402 in infants.
 - To evaluate the efficacy of AERAS-402 in the prevention of TB in infants
- Secondary Objectives
 - To evaluate the immunogenicity of Ad35.TBS/AERAS-402 in infants compared to controls
 - To assess potential immune correlates of protection from TB in infants vaccinated with Ad35.TBS/AERAS-402

Phase IIb Proof of Concept Study in Infants

- Study C-029-402: Phase II, Double-blind, Randomized, Placebo-controlled, Multicenter, Proof-of-concept Study of Ad35.TBS/AERAS-402 in BCG-vaccinated, HIV-uninfected Infants Without Evidence of Tuberculosis (age =16-26 weeks)
- *Divided in two phases:*
 1. Dose finding phase (in Kenya)
 2. Safety and efficacy phase in up to 4,096 infants (currently planned at 4 sites in Uganda, Kenya, Mozambique and South Africa)

Phase IIb Proof of Concept Study in Infants

- Study C-029-402: Dose finding Phase (Kenya)
 - Three dose levels will be investigated in 192 subjects
 - Infants will be randomized in a ratio of 3:1 to receive two doses of Ad35.TBS/AERAS-402 or placebo, on Study Day 0 and on Study Day 28
- The highest dose level with acceptable safety and immunogenicity will be selected to proceed with the safety and efficacy phase

Ensuring global delivery

Intensifying rAd vaccine manufacturing at Crucell



- Developing world birth cohort of $\approx 100,000,000$



USP

- Bioreactor 500L
- Harvest 10^{12} vp/mL
- Batches/Yr ~ 45
- Doses/Yr $> 100,000,000$

The Crucell AdVac Process Intensification Initiative intends to establish rAds as vectors for global scale delivery

Increases in Unit/Volumetric Productivity

Single Use Disposability

PER.C6®

For World Vaccine delivery



20,000L Stainless Steel



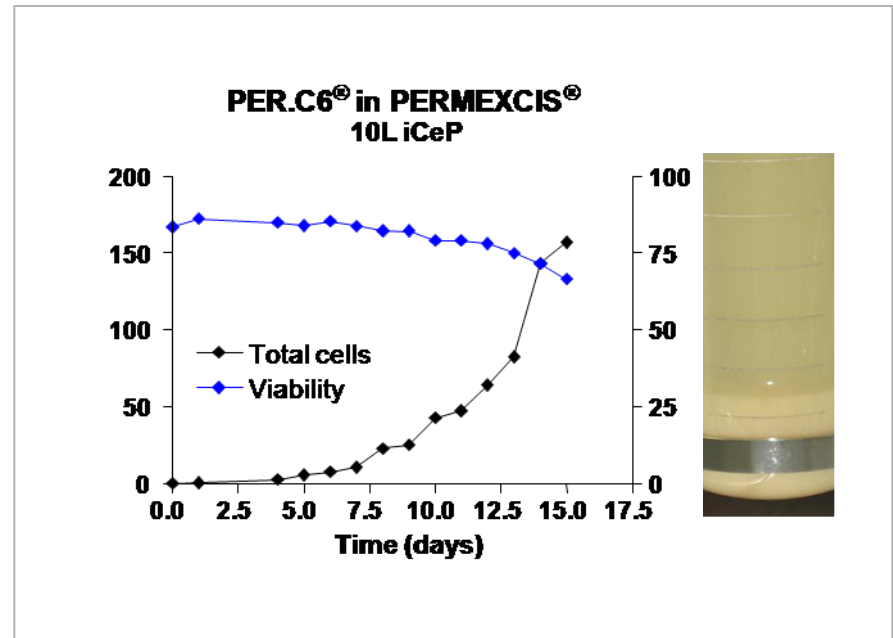
Growth SF in suspension
without adaptation
as single cell suspensions



Cell growth to
150,000,000 cells/mL

High density PER.C6® cell culture (> 15×10^6 cells/mL) will be used in process intensification for rAd **vaccine** production

PER.C6[®] Grow to Very High Density in XCellerex Bioreactors Supported with ATF Perfusion



Crucell boost for rAd Manufacture: intensified Manufacturing for Adeno Production (iMAP)



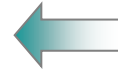
PER.C6®

iMaP



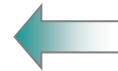
- **Intensify USP**

- **Cell Density** **10x**
- Bioreactor 500L
- Harvest ~10x



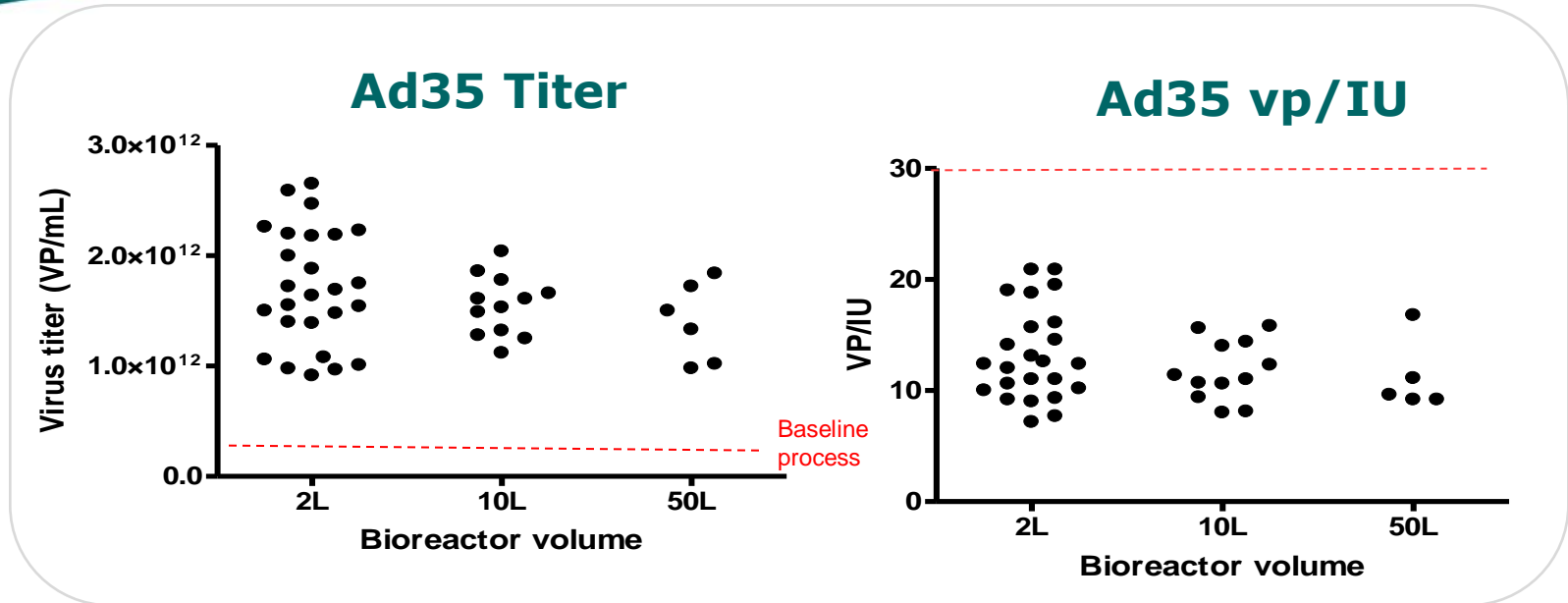
- **Reduce Mfg Cycle Time**

- **Batches/year** **~2x**
- Doses/year ~20x



Scale-up run of the iViP process

10 fold Increase Compared to the Baseline Process



Successful scale-up of iViP process to 50L scale into disposable bioreactor systems

No change in VP/IU ratio compared to standard process

A new Perspective on rAd Manufacturing

Intensified Manufacturing for Adeno Production



- Bioreactor 500L
- Harvest $\sim 1.5 \times 10^{12}$ vp/mL
- Process Yield $\sim 50\%$
- Vial Fill 10^{11} vp
- Batches/Yr ~ 45

BioReactor	50L	500L
Doses per Batch	0.37 MM	3.75 MM
Doses per year	16 MM	168 MM



Acknowledgments



- Alfred Luijstens
- Marcel de Vocht
- Claire Stoekle
- Alain Pralong
- John Lewis
- Sandra Kik
- Frances Burghouwt
- Maria Grazia Pau
- Jaap Goudsmit



- Donata Sizemore
- Macaya Douoguih
- Bernard Landry
- Sean Bennett
- Margaret Goetz
- Jacqueline Gearhart
- Eloi Kpamegan
- Robert Walker
- Bruce McClain



- Brian Abel
- Hassan Mahomed
- Gregory D Hussey
- Willem A Hanekom



- D Bateman
- M E Bateman



SAINT LOUIS
UNIVERSITY

- Daniel F. Hoft



Combating infectious diseases



by bringing innovation to global health