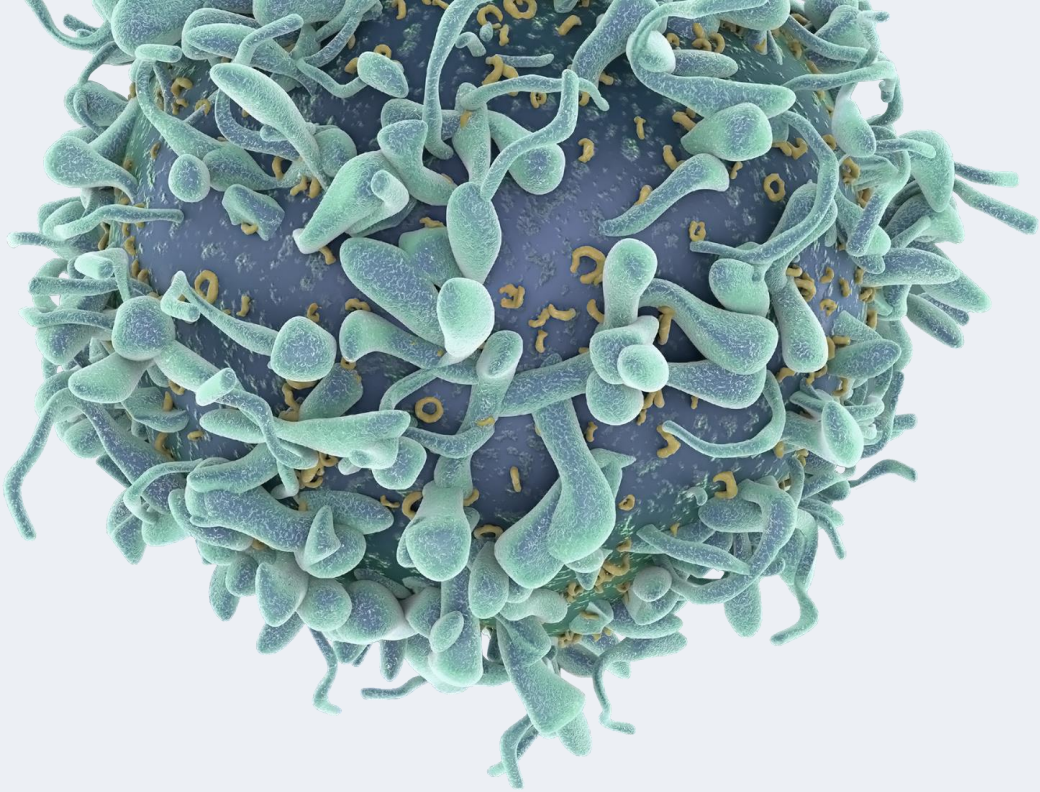


VIR-2020: a CMV-based vaccine candidate for TB

Aurelio Bonavia

February 21, 2018, TB Global Forum, New Delhi, India

INFECTIOUS DISEASES Massive Unmet Need

2,000,000,000	People latently infected with tuberculosis
260,000,000	People living with chronic hepatitis B
37,000,000	People infected with HIV
2,000,000	Number of antibiotic resistance cases annually in US
240,000	Number of hospitalizations for RSV annually in US
36,000	Number of deaths from flu in the US

Source: World Health Organization (WHO), U.S. Center for Disease Control (CDC)

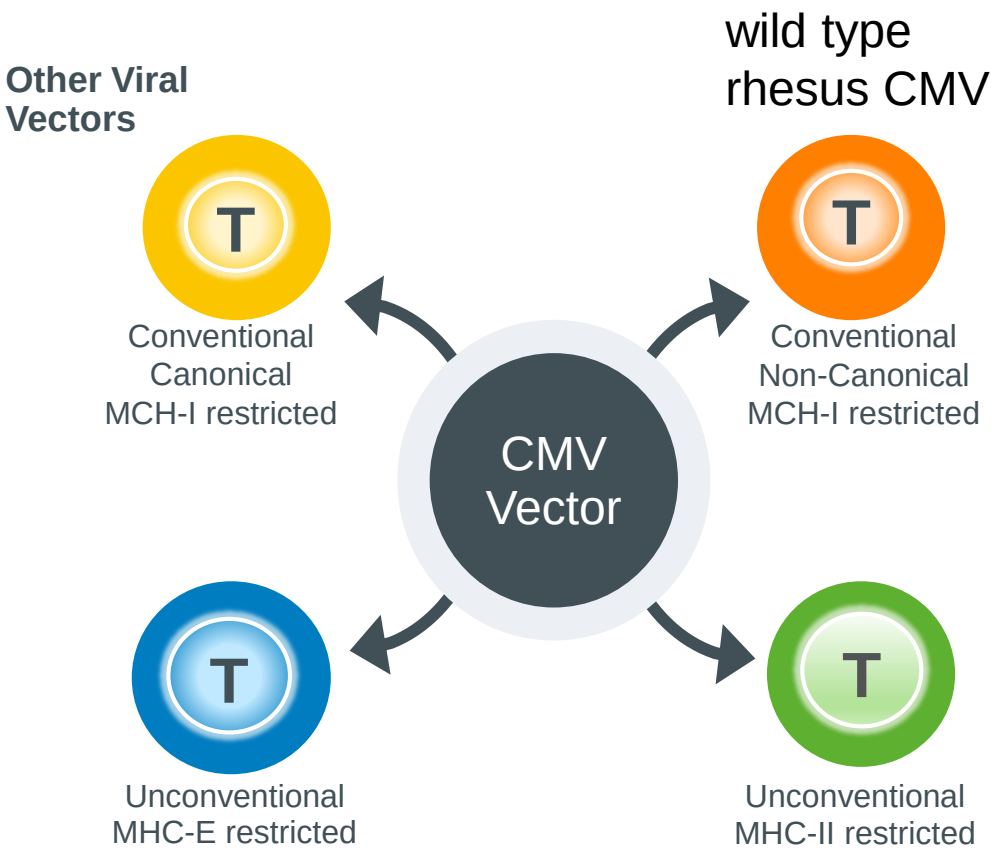
IMAGINE A WORLD WITHOUT INFECTIOUS DISEASES

- Private company headquartered in San Francisco (CA) with locations in Portland (OR), Boston (MA), and Bellinzona (Switzerland)
- Major partnership with Bill and Melinda Gates Foundation for development of HIV and TB vaccines
- Our mission is to utilize advances in science, technology, and medicine to transform the care of people with or at risk of serious infectious diseases inclusive of low and middle income countries (LMIC)
- Current programs focus on: TB, HIV, chronic hepatitis B, respiratory viruses (Influenza, RSV, HMPV, PIV)

CMV Vector: Unique candidate vaccine features

- Re-infection and persistence are common despite pre-existing CMV immunity
- Profound attenuation (titers, tropism, spread and shed)
- Our CMV vectors elicit strong immune responses:
  - Long-term maintenance of high frequency of effector memory T cells
  - T cells are maintained in organs (including mucosal and lymphoid tissues) regardless of route of administration
  - Programmable CD8+ T cell response (expanded breath, MHC-II and HLA-E restriction)

Using CMV Specific Deletions: Non-overlapping CD8+ T cell responses are programmable



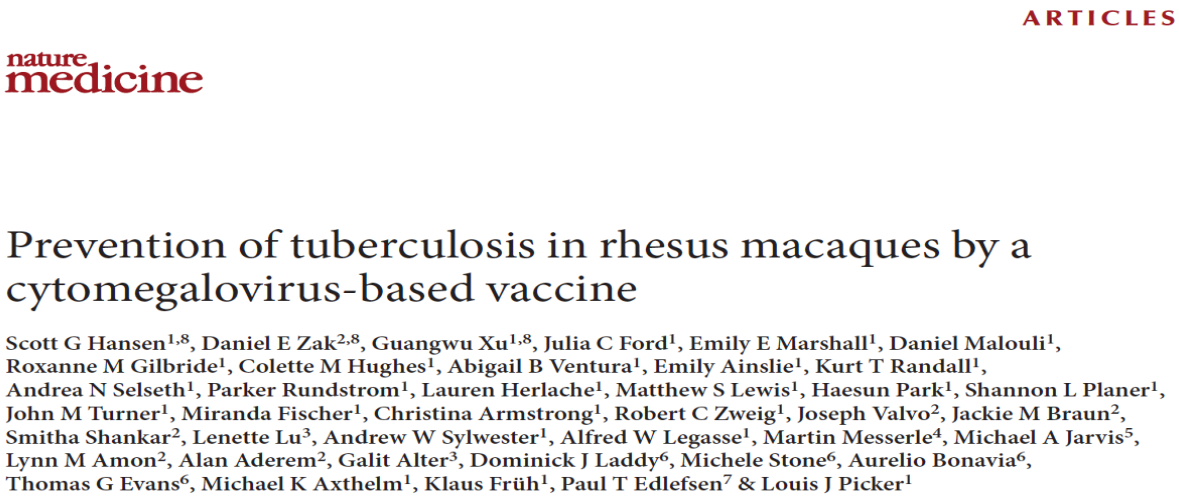
- CXC chemokine-like proteins

UL146/147

UL128/130

- Pentameric complex
- Tropism (required for entry in epithelial and endothelial cells but not for fibroblasts)

Proof of Concept in Rhesus Macaques



ARTICLES

nature medicine

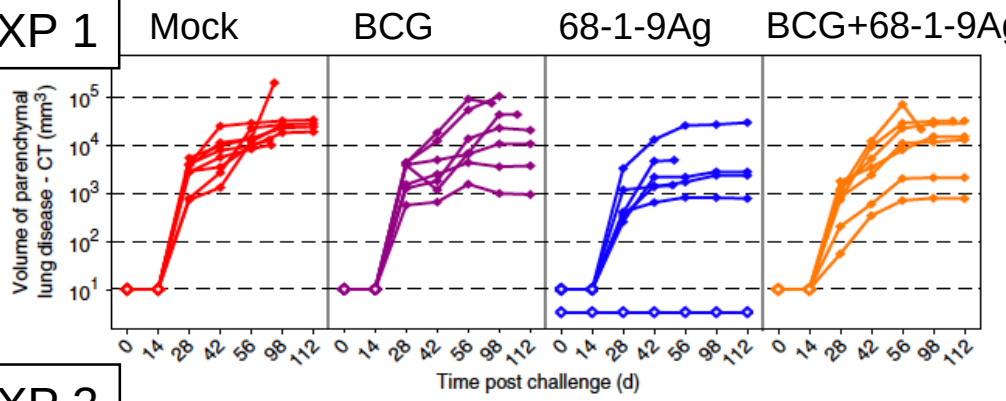
Prevention of tuberculosis in rhesus macaques by a cytomegalovirus-based vaccine

Scott G Hansen[1,8], Daniel E Zak[2,8], Guangwu Xu[1,8], Julia C Ford[1], Emily E Marshall[1], Daniel Malouli[1], Roxanne M Gilbride[1], Colette M Hughes[1], Abigail B Ventura[1], Emily Ainslie[1], Kurt T Randall[1], Andrea N Selseth[1], Parker Rundstrom[1], Lauren Herlache[1], Matthew S Lewis[1], Haesun Park[1], Shannon L Planer[1], John M Turner[1], Miranda Fischer[1], Christina Armstrong[1], Robert C Zweig[1], Joseph Valvo[2], Jackie M Braun[2], Smitha Shankar[2], Lenette Lu[3], Andrew W Sylwester[1], Alfred W Legasse[1], Martin Messerle[4], Michael A Jarvis[5], Lynn M Amon[2], Alan Aderem[2], Galit Alter[3], Dominick J Laddy[6], Michele Stone[6], Aurelio Bonavia[6], Thomas G Evans[6], Michael K Axthelm[1], Klaus Früh[1], Paul T Edlefsen[7] & Louis J Picker[1]

- Two NHP studies showed protection against low dose challenge with Mtb Erdman (Hansen *et al.*; 2018)
  - 41% of animals showed no TB disease by CT scan and necropsy
  - Overall 70% reduction in TB infection/disease (lung and extra-pulmonary disease)
  - Unconventional immune response is not required for TB protection

Efficacy in NHPs: Challenge study with Mtb after vaccination with RhCMVs

EXP 1

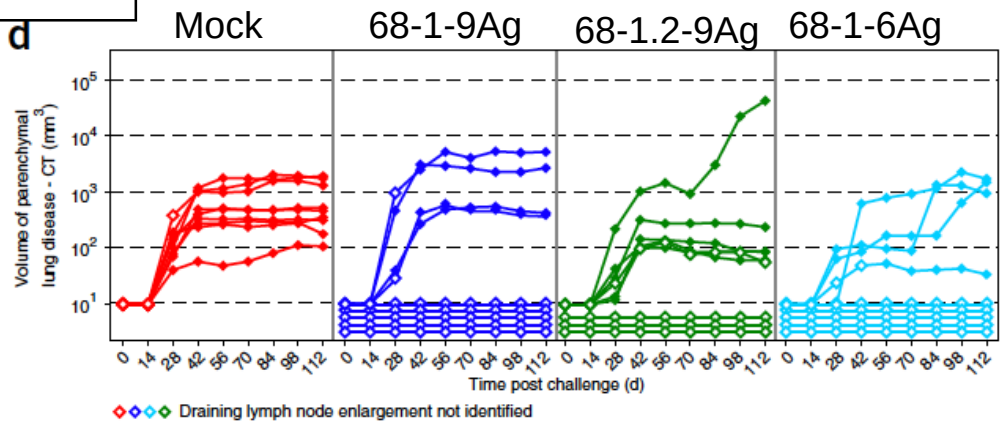


25 CFU Mtb Erdman intrabronchial (IB)
Poisson modeling

- 68.7% Mtb recovery and 67.3% based on pathology score against placebo
- 57.7% and 51.4% against BCG

EXP 2

d



10 CFU Mtb Erdman IB
Poisson modeling

- 5/9 (68-1-9A); 3/8 (68-1.2-9Ag); 5/9 (68-1-6Ag) had no sign of disease
- 9Ag and 6Ag gave similar protection with 68-1

6 Ag fusion protein: Ag85A- ESAT-6-Rv3407- Rv2626-RpfA-RpfD
9 Ag: 4 vectors encoding the 6Ag + Ag85B + Rv1733 + RpfC
rhCMV 68-1: UL128/130 deleted, fibroblast tropic and unconventional immune response
rhCMV 68-1.2: UL128/130 repaired and conventional immune response

Nature: Hansen *et al.*, 2018

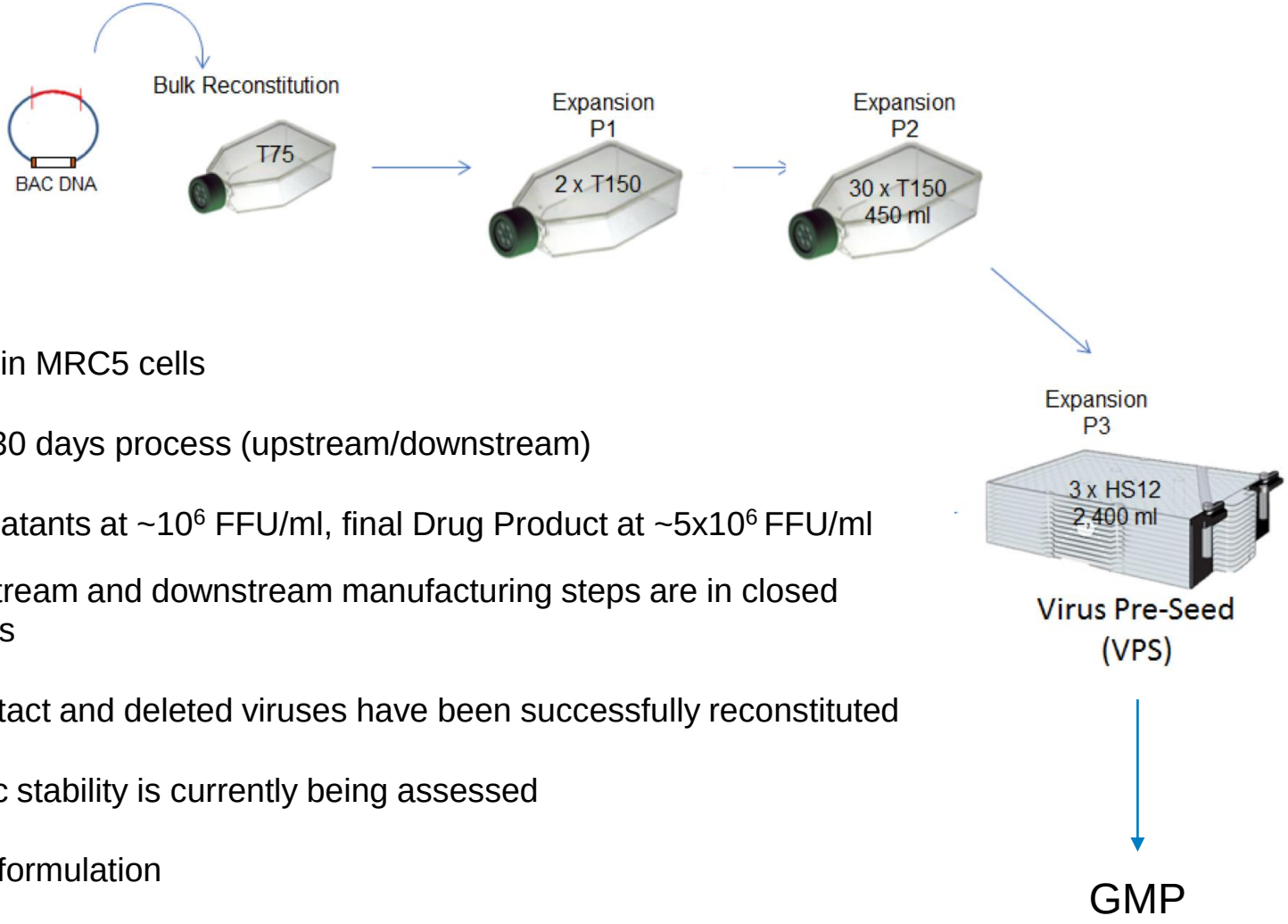
Transcriptomics

- Innate response to Mtb challenge is modified in rhCMV/TB protected rhesus macaques
    - The 28d after Mtb challenge signature (IFN module) was predictive of outcome at necropsy
    - TB-disease associated transcriptional signature was profoundly reduced in the vast majority of rhCMV/TB vaccinated animals with complete MTB control
- Correlate of protection; combined innate and adaptive immunity
    - The signature of genes preferentially expressed by neutrophil degranulation and innate immunity in vaccinated animals prior to challenge delineates the protection of vaccinated animals

VIR-2020: Characteristics of the human CMV vector expressing Mtb antigens

- Antigens: 6 Ag fusion proteins (Ag85A, ESAT-6, Rv3407, Rv2626, RpfA, RpfD) covering active, latent and resuscitation phases of Mtb life cycle
- Vector retains CMV drug susceptibility
- Deletion of UL82 (pp71)
  - Important for immediate early (IE) gene expression
  - MOI dependent *in vitro* growth attenuation
  - Human CMV-Δpp71 does not reactivate in a humanized mouse model
  - Rhesus CMV-Δpp71 does not shed in NHP urine
  - Rhesus CMV-Δpp71 is deficient in spread (no spread to organs, no transmission to cohabitating animals and no transmission through leukocyte transfer)
- Additional safety measure: incorporation of miR124 micro-RNA sequence which prevents CNS replication
- Deletion of UL128/130 which renders the virus fibroblast-tropic confers further attenuation

Some Key Features of Manufacturing



- Grown in MRC5 cells
- About 30 days process (upstream/downstream)
- Supernatants at ~10^6 FFU/ml, final Drug Product at ~$5x10^6$ FFU/ml
- All upstream and downstream manufacturing steps are in closed systems
- Both intact and deleted viruses have been successfully reconstituted
- Genetic stability is currently being assessed
- Stable formulation

Plan for First in Human Trial

- Phase 1 in healthy adult volunteers (non-BCG vaccinated, QFT-, HIV-, CMV+)
- Double-blind placebo controlled study
- Dose escalation and expansion
- Two 12 week apart subcutaneous doses with six month follow up after second dose
- Endpoints
  - Primary endpoints: *Safety* including shedding in blood, urine and saliva
  - Secondary endpoint: *Immunogenicity* (CD4+/CD8+, conventional/unconventional and antibodies to insert-specific TB-6Ags
  - Exploratory endpoints: Biomarkers/transcriptomics, immune response characterization

Tentative Timelines

- **2018**

  Process development, analytics, stability and generation of Virus Pre-Seed

- **2019**

  Vector selection and GMP manufacturing

- **2020**

  First-in-human

Thank You!

OHSU

Marcel Curlin
Klaus Frueh
Scott Hansen
Louis Picker
Eric Vela

IAVI

Coreen Booth
Eddy Sayeed

Aeras

Danny Casimiro
Agnes Chenine
Tom Evans
Ann Ginsberg
Dominick Laddy
Polly Limbach
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Vir-SF Team

The End of the Beginning