BILL & MELINDA GATES foundation

LOST IN TRANSLATION: DATA AS THE COMPASS TO SUCCESS

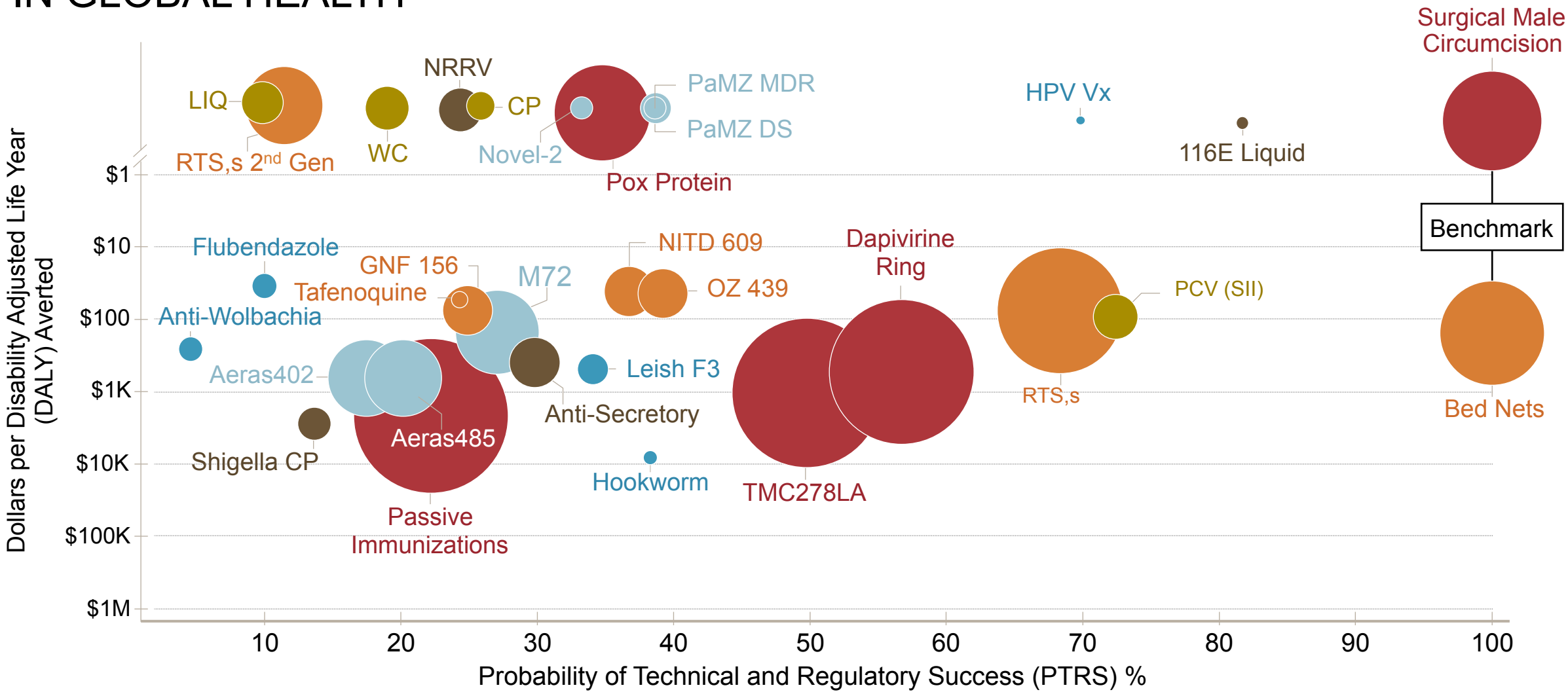
Dr. Trevor Mundel, *President, Global Health*

THE PROBLEM

We have a vast portfolio of ideas and proto-solutions.

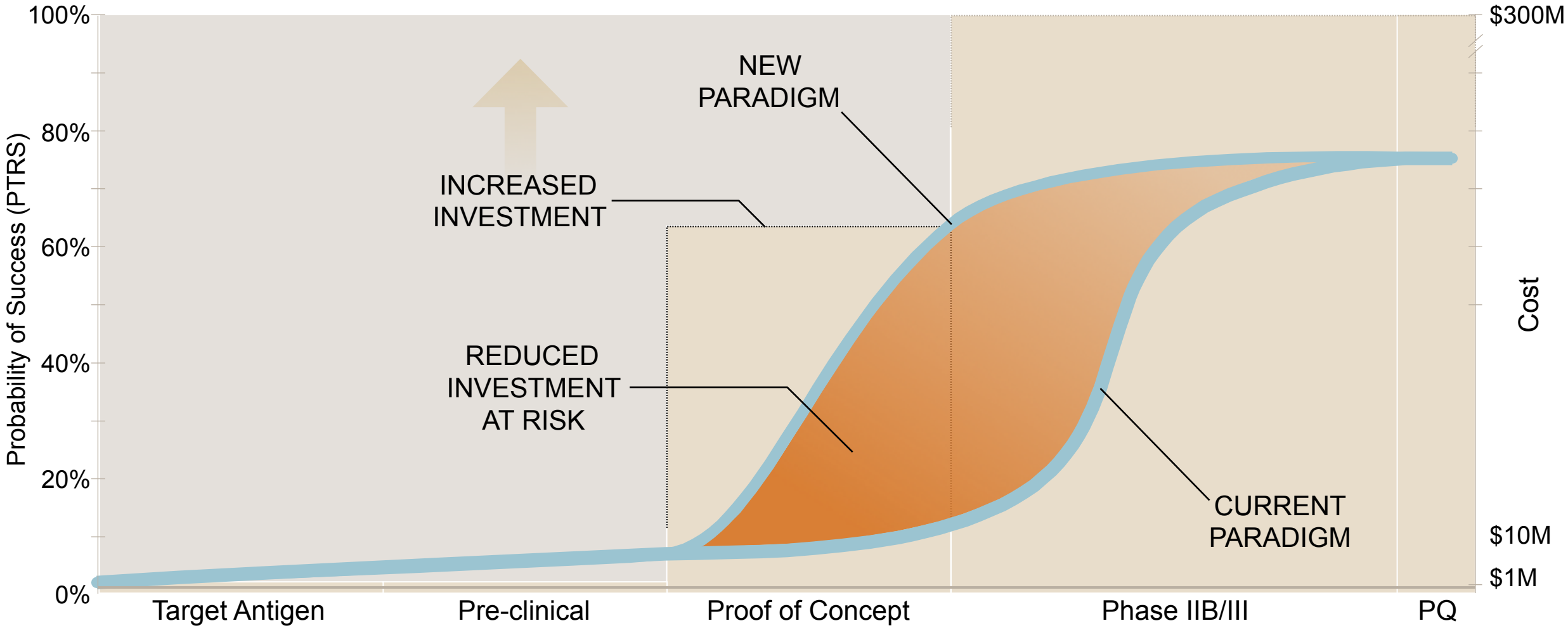
Linking the ecosystem of partners with the tools and platforms necessary to accelerate impact is central to our efforts going forward.

GUIDING OUR INVESTMENTS IN GLOBAL HEALTH

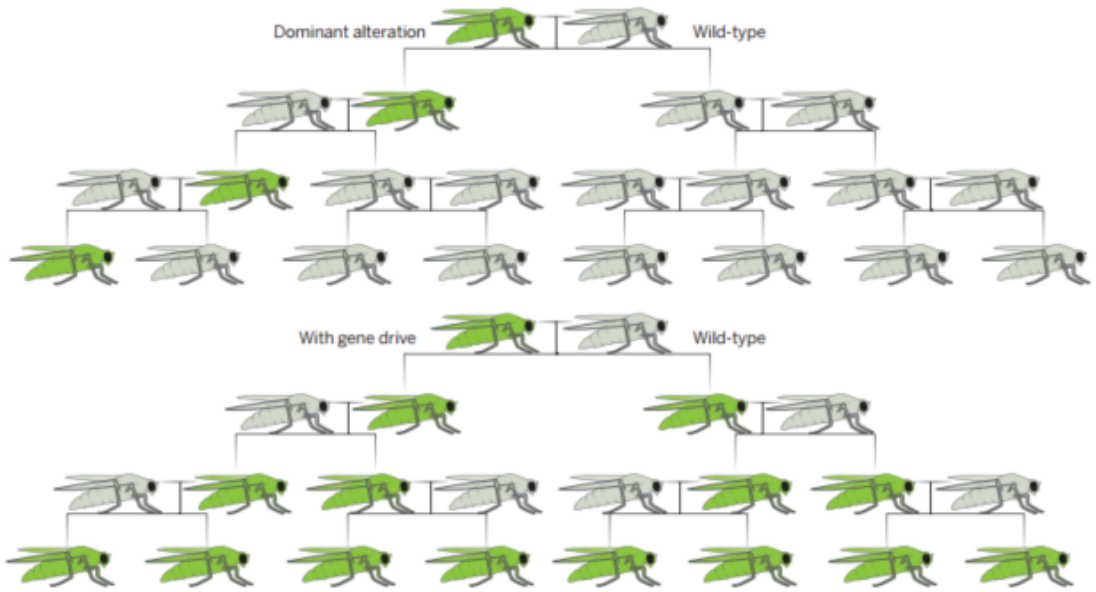


THE FUNDAMENTAL CHALLENGE

HOW TO ALLOCATE RESOURCES TO PROGRESSING THE PORTFOLIO IN A MANNER THAT MAXIMIZES SPEED AND FINDS THE HIGHEST VALUE OPPORTUNITIES (MINUS RISK OF LATE FAILURE).



SAFEGUARDING GENE DRIVE EXPERIMENTS IN THE LABORATORY



The spread of RNA-guided gene drive systems. Unlike the population dynamics of normal genomic alterations, gene drive systems can spread changes through wild populations by converting heterozygotes into homozygotes in each generation.

BIOSAFETY

Safeguarding gene drive experiments in the laboratory

Multiple stringent confinement strategies should be used whenever possible

Science

4 October 2002

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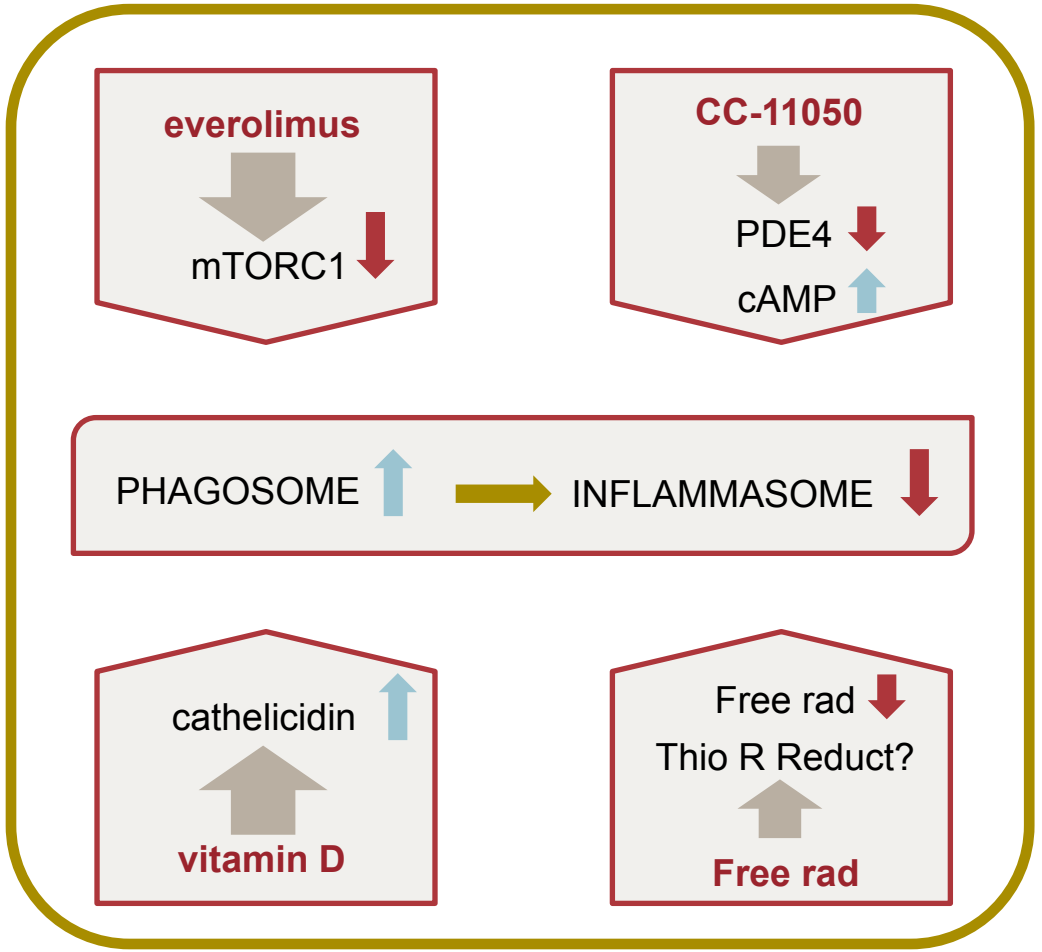
Pages 1–310 $10

THE MOSQUITO GENOME
Anopheles gambiae

PROOF OF CONCEPT: TB HOST DIRECTED THERAPY

Shorten treatment and minimize lung damage by increasing autophagy and decreasing inflammation.

- First set of interventions: vitamin D, CC-11050, everolimus, and auranofin
- HDT will be added for 4 months to standard therapy in DS TB patients, and compared to standard therapy alone
- Goal of the trial
  - Establish safety
  - Indications of mechanistic effect, plausibility of efficacy
- Variety of endpoints
  - Traditional bacteriological
  - PET/CT Lung Imaging
  - Lung function
  - Biochemical assays based on mechanism
  - Biomarkers of response

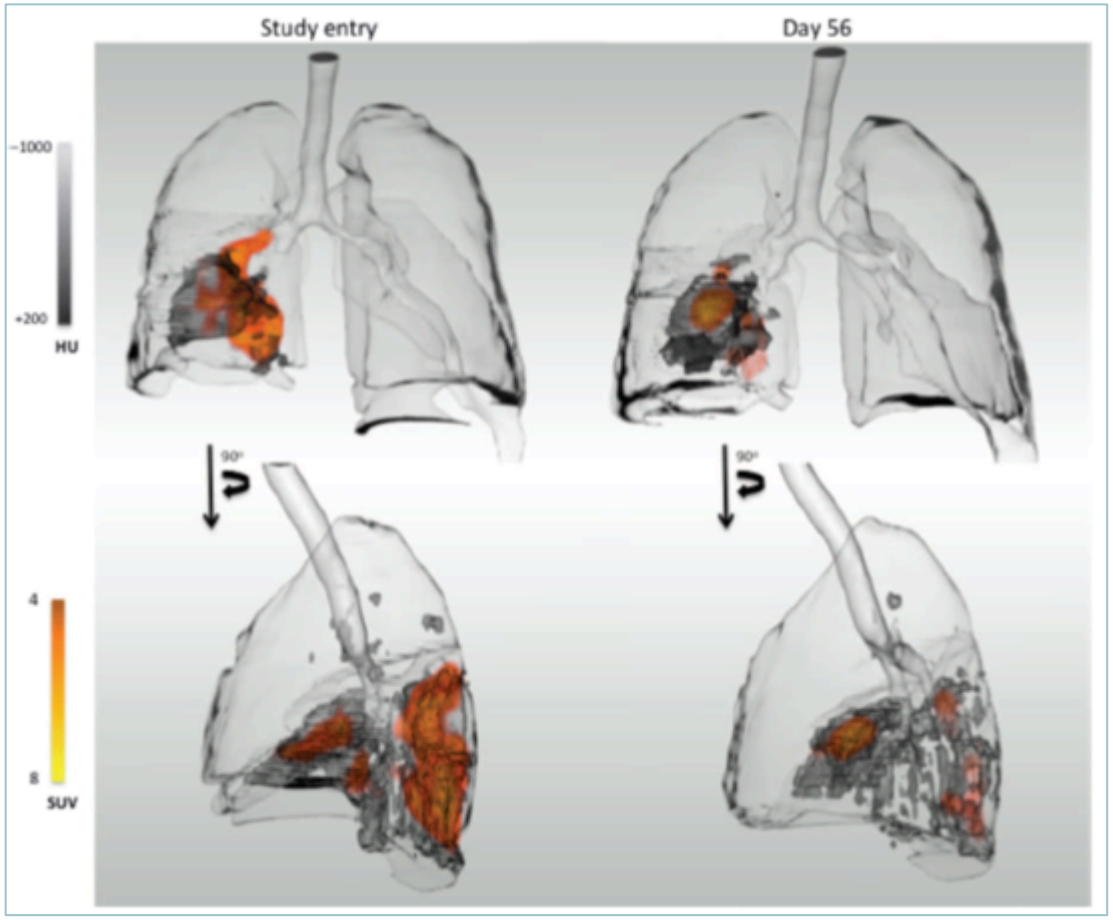


PROOF OF CONCEPT: PET/CT SCANNING IN TB PATIENTS

Scanning in TB patients show heterogeneous response within the lung.

CT

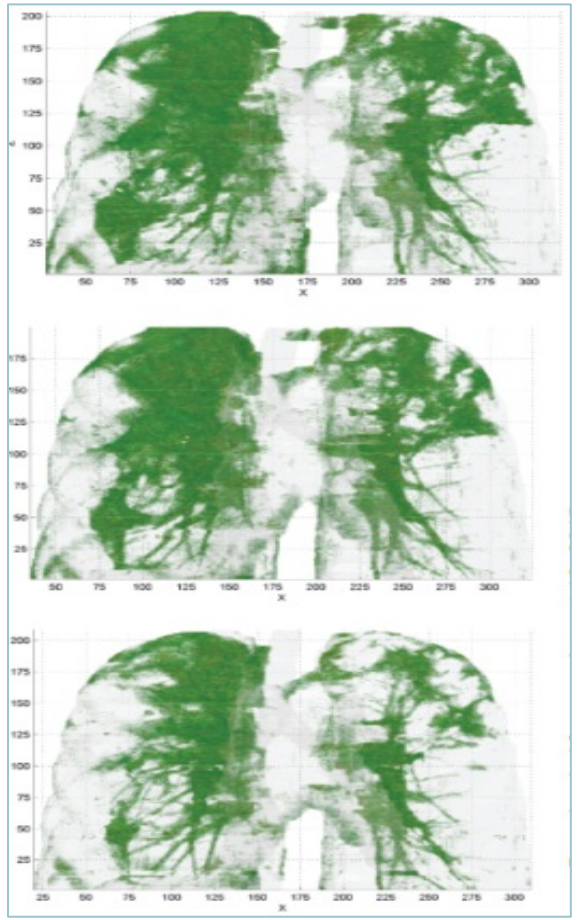
FDG PET



Start of treatment

2 months

6 months

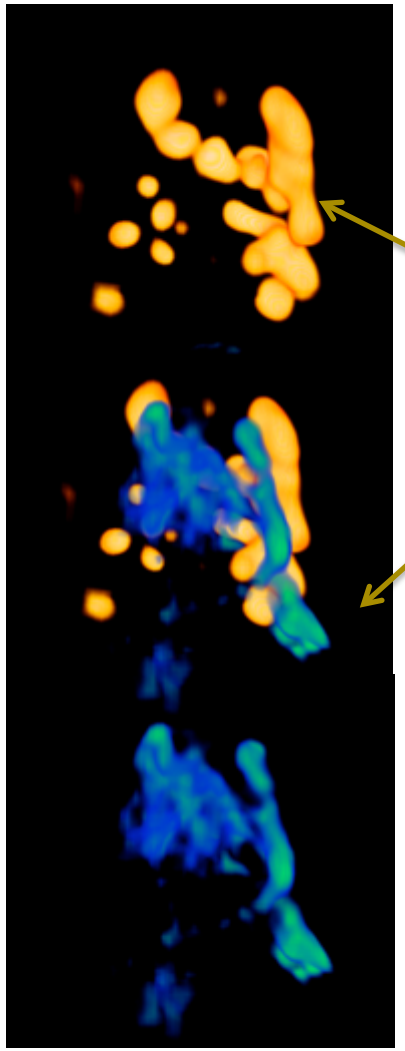


PET IMAGINE COULD PROVIDE AN EARLY SIGNAL OF EFFICACY IN HOST DIRECTED THERAPY

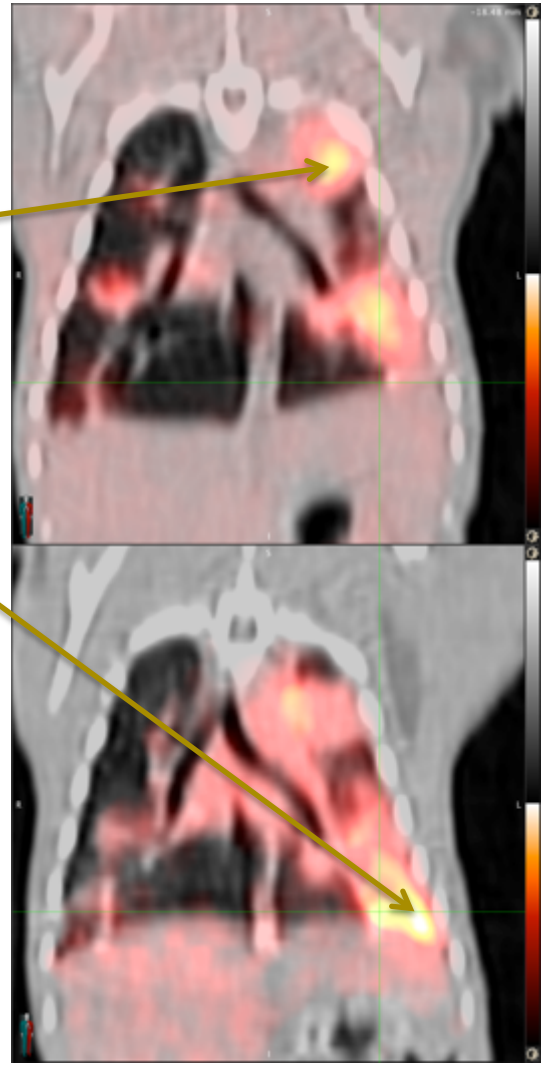
FDG

Registered (based on CT)

FDT

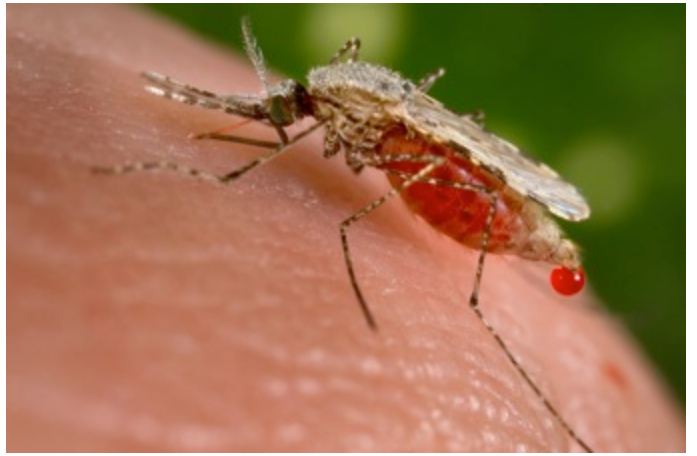


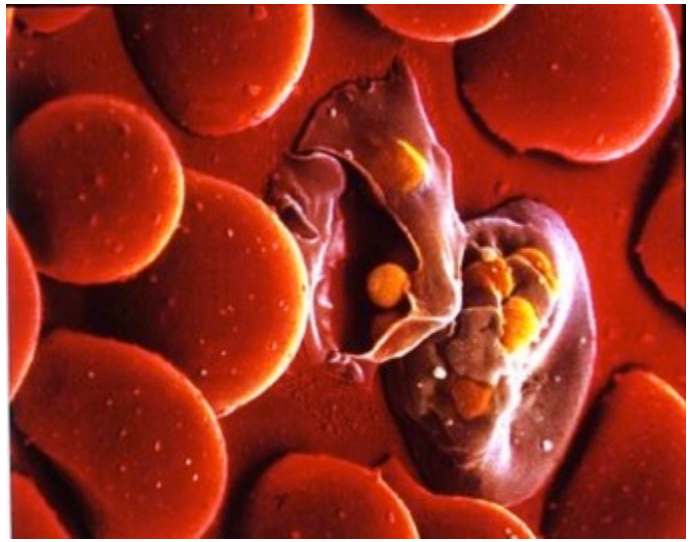
Lesion at diaphragm shows differential labeling pattern



THE HUMAN CHALLENGE: MALARIA

- Volunteers inoculated with ~1,800 viable Plasmodium falciparum-infected human erythrocytes
- Daily qPCR
- After approx 6 days parasite levels reach 1000 p/ml
- Start treatment
- F/U until 28 days
- Human model decreases risk and improve decisions
- Response in sub-clinical infection reflects clinical reality





THE HUMAN CHALLENGE: MALARIA

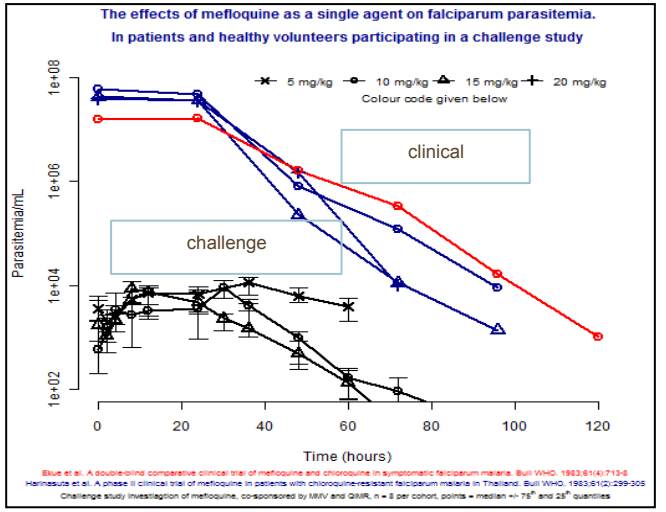
~1,800 malaria-infected Red Cells by IV injection

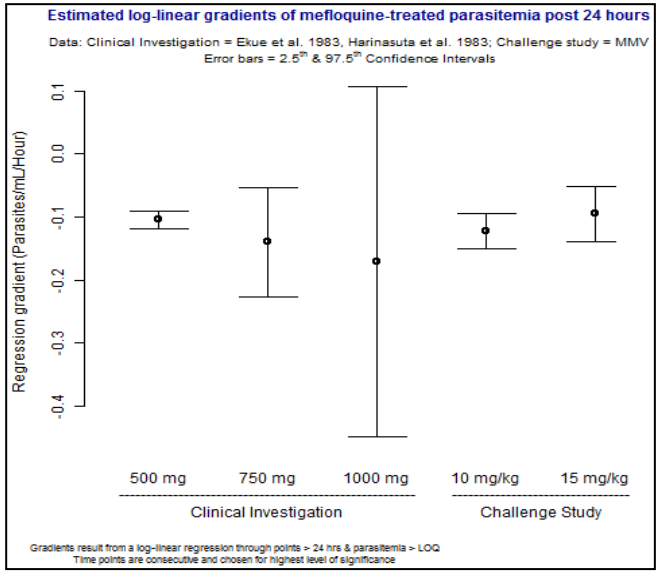
Discharge ≥ 36 hr after dosing if clinically stable

Day	0	1	2	3	4	5	6	7	8	9	10	11	12		28
Outpatient	Inoculation	X	X	X	X	X	X	X			+/-	X	X	X	X
Confinement															
Drug Rx															
PK									XXXXXXXX						
PCR				X	X	X	X	X	XXXXXXXX			X	X	X	X

Drug administration:
- PCR ≥ 1,000 parasites/mL
- Malaria symptoms

? Rescue Drug Rx



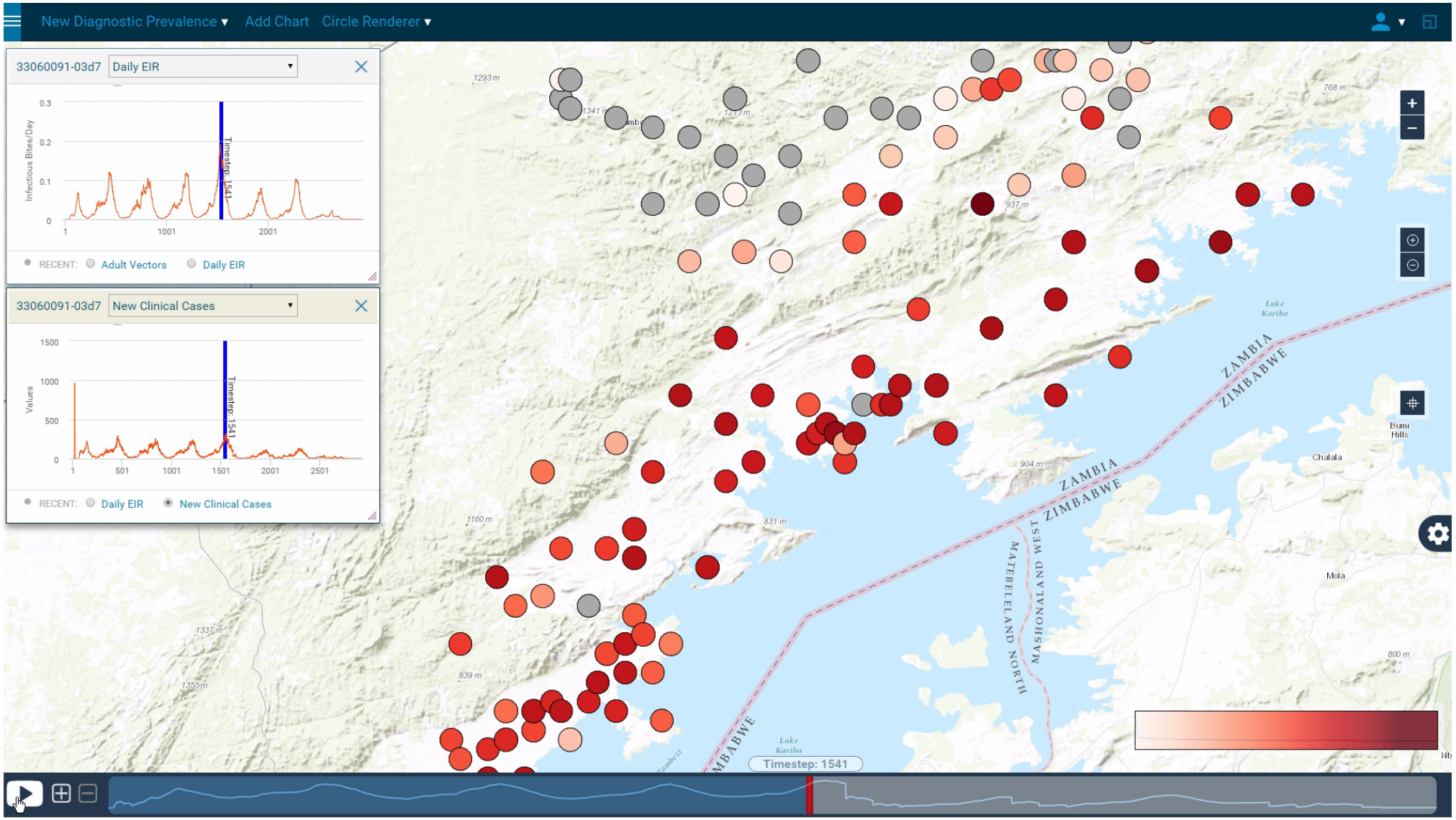


HEALTHY BIRTH, GROWTH, AND DEVELOPMENT

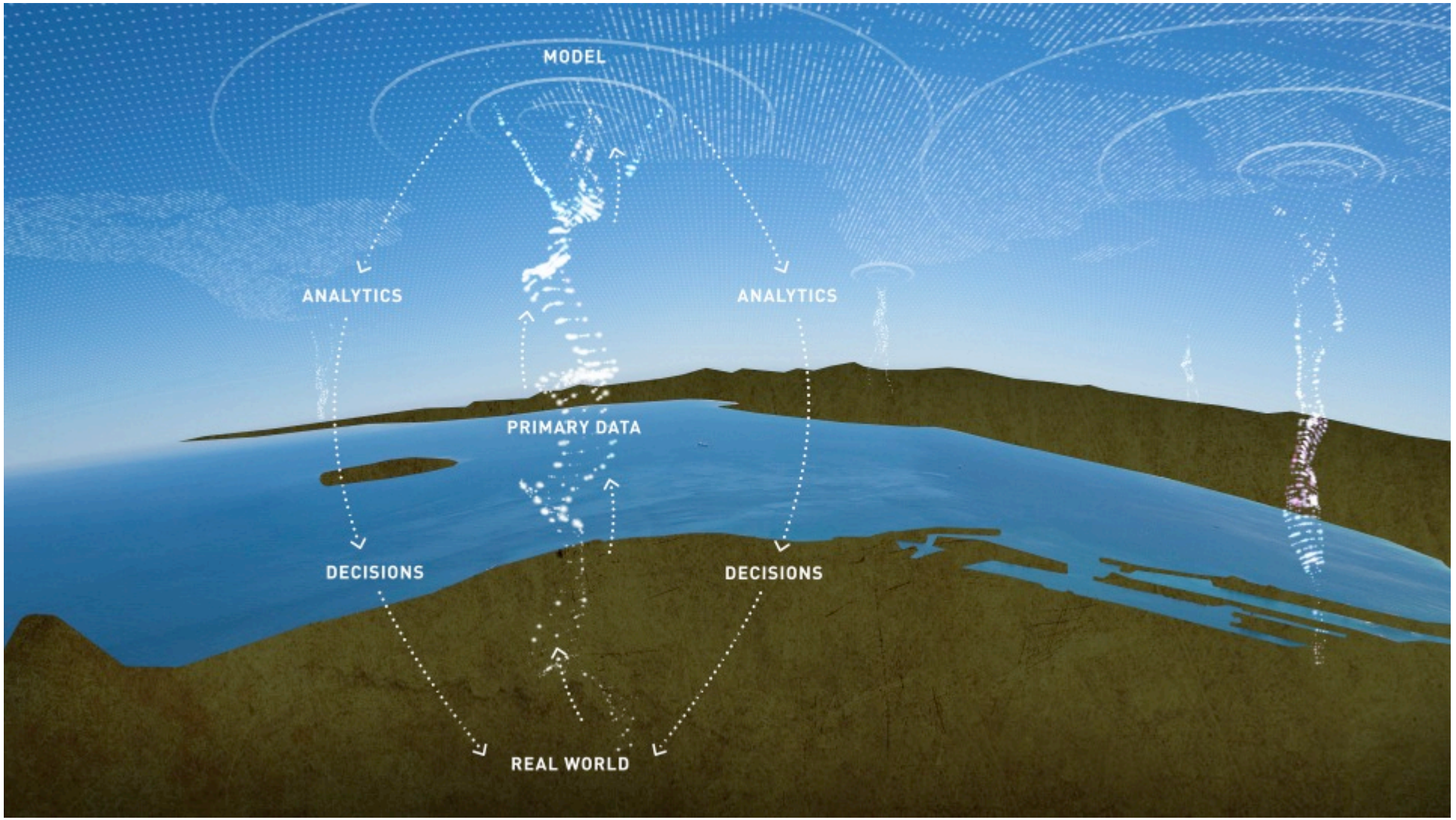
The WASH Benefits study will measure the impact of water, sanitation, hand washing and nutritional interventions during the first 2 years of life in rural Bangladesh and Kenya.

- Trials will include 7 arms:
  - Water quality
  - Sanitation
  - Handwashing
  - Water quality + sanitation + handwashing
  - Nutrition
  - Nutrition + water quality + sanitation + handwashing
  - Double-sized control arm

TRANSLATION: LARGE-SCALE DYNAMIC MODELING OF DISEASES



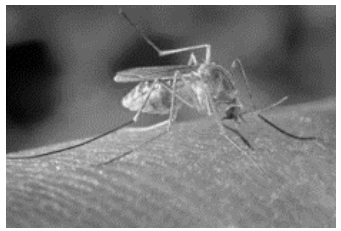
SUCCESS IN TRANSLATION




THE WORK IS
COMPLICATED.
WHY WE DO IT IS NOT

TRANSLATION EXAMPLE: WOLBACHIA

- Naturally occurring bacteria
- Lives inside insect cells
- Occurs naturally in up to 60% of all insect species
- Transmitted from parent to offspring through the insect's eggs
- Not naturally found in Aedes aegypti mosquito
- Cannot be transmitted to warm-blooded animals
- Safe for humans, animals and the environment

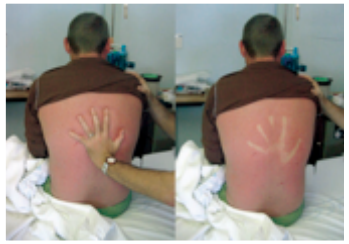


CRITERIA	MINIMUM ACCEPTABLE	*w*MEL Candidate
Inhibition of viral transmission	>50% reduction in virus prevalence in saliva	60-75% for DEN 1-4
Invasiveness	Short term release(s): >95% invasiveness	✓
Sustainability	90%+ sustained invasion	>90% in 7 sites; on track in 5 sites
Maternal transmission	≥95%	100%
Cytoplasmic incompatibility	≥95%	100%
Fitness cost	Overall fitness cost < 30%	15-25%
Wolbachia density	Higher in critical tissues (e.g., salivary glands)	✓
Effect on other arboviruses	No transmission enhancement of other pathogens	No enhancement
Modelling predictions	Local elimination	Local elimination

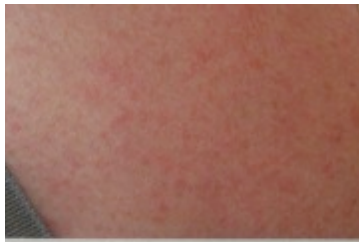
CHALLENGE MODEL EXAMPLE: DENGUE HUMAN CHALLENGE

Model Characteristics

- Based on an avirulent natural isolate
- Repurposed 'hot' vaccine candidate
- Healthy volunteers
- Primary endpoint viraemia NOT disease model - safe
- Characterized by rash similar to natural infection
- 20-40% neutropenia
- Reproducible attack rate (100%) allowing well powered studies



Dengue Rash



Challenge strain rash DEN2 Δ 30

Uses

- Vaccine efficacy
  - e.g. NIH candidate (TV0003) tested in small CHIM EM (N=21 and 20 controls)
  - 100% protection from viraemia & neutropenia
- Correlates of vaccine protection
  - Correlates in TV0003 to be assessed (but high levels of protection may prevent)
- Correlate of natural immunity
  - Assess mechanism of natural immunity v.s. vaccine induced

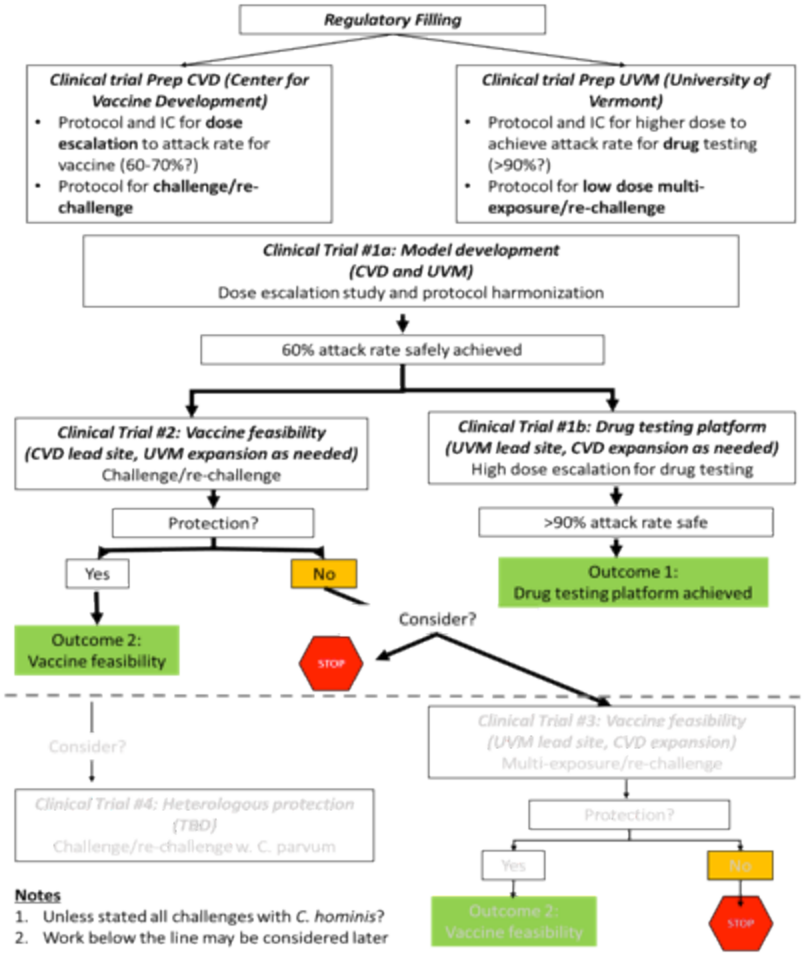
Limitations

- Over-attenuation?

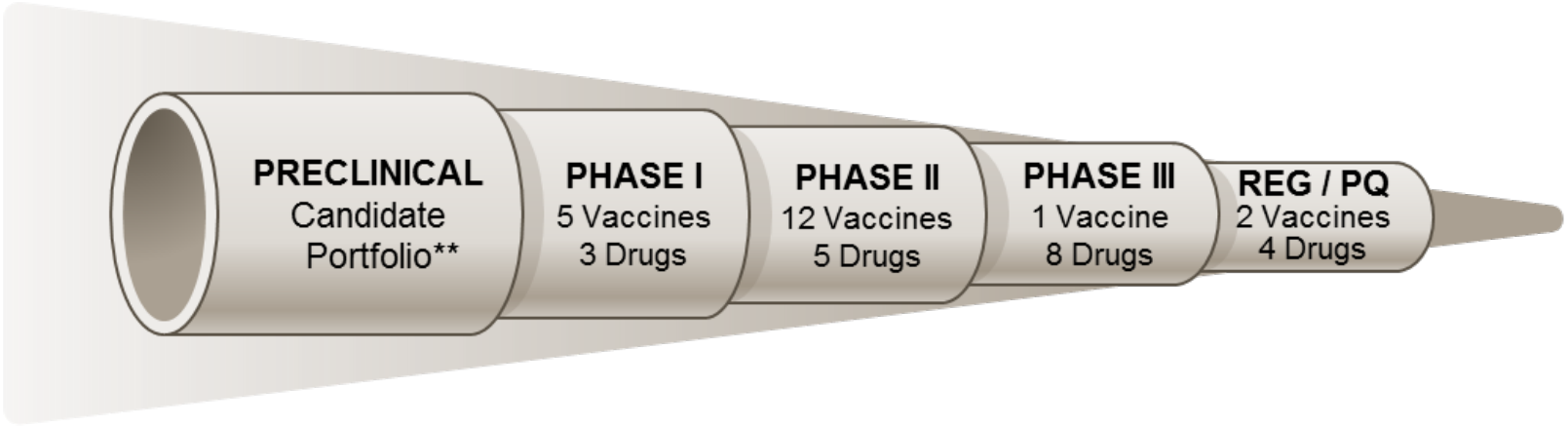
Future Directions

- Additional strains
- Development of disease model?
- Test Dengue bNAb for reverse vaccinology?

CHALLENGE MODEL EXAMPLE: CRYPTOSPORIDIUM



THE PROBLEM: WE HAVE A VAST PORTFOLIO OF IDEAS AND PROTO-SOLUTIONS



HIV/AIDS | Malaria | TB | Pneumonia | EDD | NTD | Polio | Family Planning | MNCH

*Does not include diagnostics or vector control interventions, or new combinations/regimens of licensed products

**30 preclinical candidates in development in addition to candidates and probes in Discovery

PH I: VACCINES
H56 | VirG | NRRV | Pfs25 | P5 Dev. Track

PH I: DRUGS
TBA-354 | OxSCYX 7158 | MMV048

PH II: VACCINES
ETVAX | FTA | RotaVaC 5C | RV3-BB | RTSSfd | WCV | LAIV2- | RSV-1 | PCV-10 | Alum-IPV | H4 | M72

PH II: DRUGS
TMC278 | OZ 439/PQP | DSM265 | KAE609 | BPaZ

PH III: VACCINES
BRV-LYO

PH III: DRUGS
DPV | d4T (20 mg) | TNF | Tafenoquine | DPped | Fexinidazole | BPaL | PaMZ

REG/PQ: VACCINES
Euvichol | RTSS

REG/PQ: DRUGS
Generic DMPA | NES/EE combined vag ring | Sino-Implant | PAped

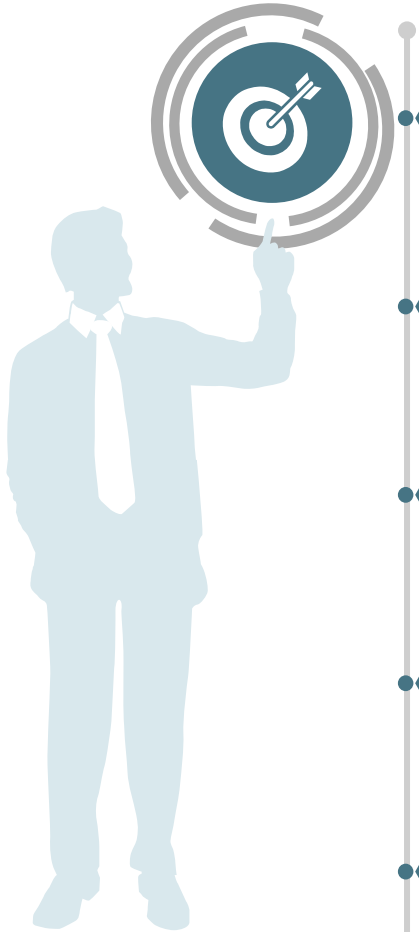
 |

CHALLENGE MODEL APPROACH

OVERVIEW SLIDE ON WHAT THE CHALLENGE MODEL IS?

- XXX
- XXX
- XXX
- XXX
- XXX

CHALLENGE MODEL EXAMPLE: CONTROLLED HUMAN INFECTIONS MODELS (CHIM) FOR ENTERIC VACCINES



- xxx
- xxx
- xxx
- xxx
- xxx

CONTROLLED HUMAN INFECTIONS MODELS (CHIMS) FOR ENTERIC VACCINES

EDD from Evan

Valuable for:

- Pathogens where we have no Correlates of Protection
- Early down-selection of candidates
- Host immune response when coupled with microarrays

Limitations

- Results in healthy adults may not translate to children
- Limited sites

EXAMPLE # 1PHASE 2B CSSBA TRIAL (CY18-19)

EDD from Evan

Rationale: Efficacy of prototype CS6 vaccine against well-defined human challenge model

Design: randomized, double-blind, placebo-controlled

Challenge strain: B7A (CS6, CS21, LT,STh,STp,O148:H28)

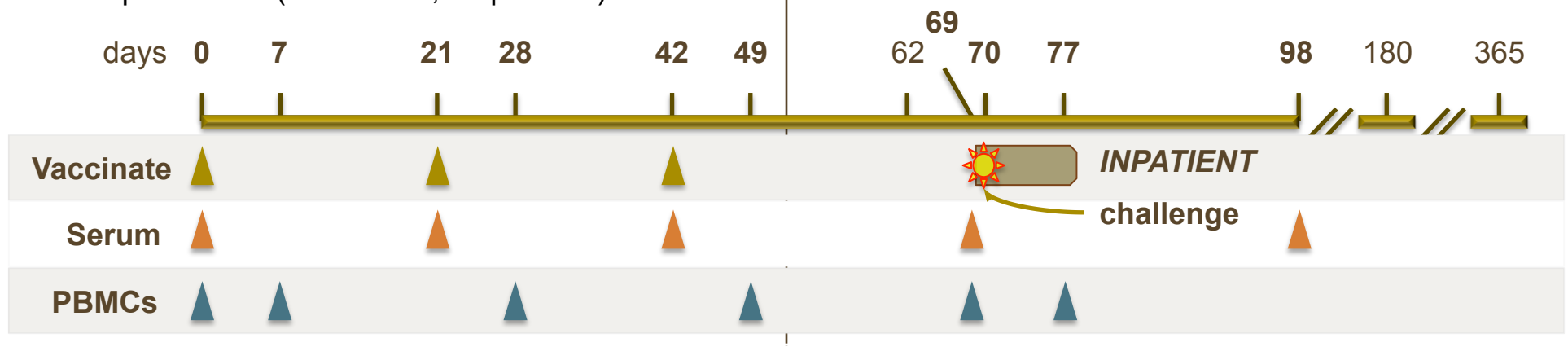
Objectives

- Primary: Efficacy against mod-sev diarrhea
- Secondary: safety and immunogenicity

Site: JHU CIR

- Sample size 56 (28 vaccine, 28 placebo)

- Pending issues/questions
  - Dose/route/adjuvant to be determined from phase 1 trial
  - B7A dose/fasting regimen defined from currently funded (DoD/PATH) efforts
  - Establish acceptable placebo response to B7A challenge a priori as a precursor to efficacy analysis
  - Identify sponsor



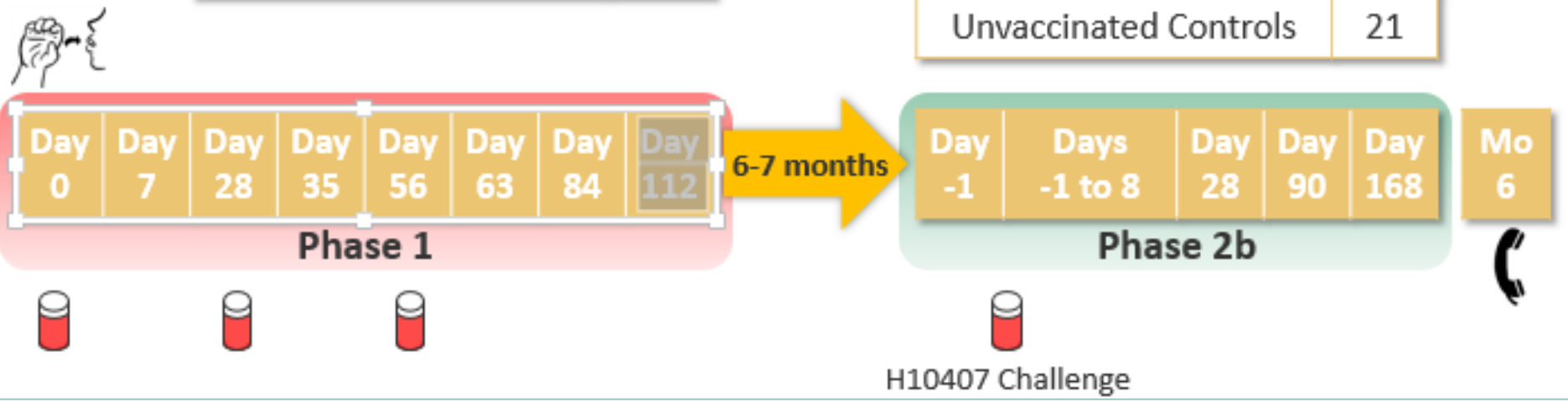
EXAMPLE #2 STUDY DESIGN AND PRIMARY EFFICACY HYPOTHESIS FOR ACE527 PHASE 2B TRIAL

EDD from Evan

Group	n
ACE527	24
ACE527 + 25 µg dmLT	24
Placebo	12

6-7 months

Group	n
ACE527	13
ACE527 + 25 µg dmLT	13
Placebo	10
Unvaccinated Controls	21



Primary Efficacy Hypothesis: The incidence of severe diarrhea will be lower in the ACE527 alone or ACE527 + dmLT recipients compared to unvaccinated controls.

Vaccine Dose: 10^{10} cfu of reconstituted lyophilized formulation (~$3x10^9$ of each strain).

INVENTORY / GAP ASSESSMENT

CHALLENGE MODELS NEEDED FOR **SHIGELLA** VACCINE CANDIDATES IN BMGF PORTFOLIO

EDD from Evan

Model	Strain	Shigella whole cell (WC Lead)	DB Fusion [6] (Sub Unit Backup)	GMMA [1]	Truncated whole cell	WRSS1 (Live Att)	CVD1208S [3]
S. flexneri 2a **CHIM from Karen K at CVD**	2457 strain Frozen seed est., dose has been determined[9]	Use current model[4]	Use current model		Use current model		no
S. flexneri 4a [7] **CHIM from Karen K at CVD** S. flexneri 6 [8]	Plate grown organism, dose to be determined				Would need sf6		no
S. Sonnei 53G **CHIM from Bob @ CCHMC Lyo**	-53G Plate grown -53G Lyo (proposed)[9]	Would benefit from a lyo 53G [5]	Would benefit from a lyo 53G	Would benefit from a lyo 53G	Would benefit from lyo 53G to show ~~cross strain~~ protection	no [2]	

1. GMMA project funding will hinge on P1 data provided in May. The GSK POC will be sonnei, but we really don't have a BMGF PoC until a flex CM. That would be late 2017
2. WRSS-1 is a live attenuated candidate with nominal BMGF preclinical funding. Other funders would carry if forward to challenge in 2019+
3. CVD1208S is not in the EVI portfolio
4. The Lead Candidate TSWC is in a program design that requires it to work first on flex 2a before progressing
5. A Challenge model using Sf2a and sonnei is planned in 2016
6. This model can predict whether cross protection exists in man, but is not essential to current vaccine development.
7. Sf6 does not cross react with other strains, so will be used to test protection against itself.
8. Dose finding completed outside EVI3
9. See note from Malbi in the notes section below.. S

Most useful
Somewhat useful
useful
Neutral
Not useful

INVENTORY / GAP ASSESSMENT

CHALLENGE MODELS NEEDED FOR **ETEC** VACCINE CANDIDATES IN BMGF PORTFOLIO

EDD from Evan

Model (Strain)	**CHIM**	**Information Provided by Model**	**ETVAX** [1] (WC Lead Product)	**FTA** (SubUnit Candidate)	**ST** [5] (Bolt on)	dmLT
H10407 (CFA/1, LT,ST)	Pre-existing standard	Protection; role of dmLT, establish whether CS6 is a protective antigen	Would provide false positive protection results[2]	Applicable, but B7A has more utility for POC against CS6 component		We have ACE527 +/- dmLT data but haven't parsed out the adjuvanticity vs antigen effect
E24377A[3] (LTST, CS1+CS3)	Development of strain already granted EVI3 = $___	Protection; contribution of anti-CS3 to protection,	Would establish protection against CS3 ETEC strain			
B7A[4] (ST,LT,CS6) -Plate grown refinement funded in EVI3 -Lyo Prep proposed in CHIM (EVI) ***From Dick @EVI***	Development of strain and challenge regimen already granted EVI3 = $___ Plate grown CHIM proposal (Lyo B7A)= $ ____	Protection with novel antigen; novel route of immunization; *contribution of CS6 to protection*	Would establish protection against CS6 ETEC strain	Future (unfunded) FTA plans would rely on B7A as the strain to establish that CS6 is a protective ETEC antigen and show value of CssbA component of FTA vaccine following active vaccination[6]		*Has LT…same problem as above*
ST TW10590 & TW10681 ***From Wilbur Chen at CVD***	EVI3 with DfiD $_____ CHIM Proposal from Chen CVD = $ ____	First demonstration of Contribution of Strain-ST to protection, which could lead to its inclusion in many vaccines	Not applicable until point at which ETVAX and ST would be combined	Applicable, but B7A has will likely become our POC study	Would be essential to prove ST offers protection	This ST only challenge would tell us if dmLT is stimulating a mucosal response when given peripherally.

1. E24377A will be used to challenge volunteers vaccinated with ETVAX only as well as ETVAX combined with TSWC. This will establish that the anti CS3 immunity is not compromised in combination. EVI would like to make sure of protection against key antigens, particularly CS6, if they don't show up in the travelers study. A study with CS6 (B7A CM) would also offer the best model to show the value of the dmLT adjuvant in the vaccine.
2. H10407 shares O78 antigen with ETVAX, so it will not be suitable for ETVAX challenge study
3. E24377A does not share O antigen with ETVAX, thus will be essential when doing a combination challenge or challenge alone in ETVAX studies
4. Could help determine the extent to which CS6 is a protective antigen and needs to be included in future ETEC vaccine formulations such as ETVAX.
5. ST would need a CM if it passes a P1 Study in 2018. If it was to be bolted on to ETVAX for instance, a CM would be needed.
6. For FTA, initial model refinement followed by passive protection studies using cows milk will be conducted with plate grown organisms (this work starts in 3Q2015) The active vaccination and challenge work will be done at a later time, and the lyophilized material should be available at that point.

Most useful
Somewhat useful
useful
Neutral
Not useful

