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

- Probability of Technical and Regulatory Success (%)
- Dollars per Disability Adjusted Life Year (DALY) Averted

Dollars per DALY Averted:
- $1M
- $100K
- $10K
- $1K
- $100
- $10
- $1

- Passive Immunizations
- Flubendazole
- Tafenoquine
- GNF 156
- M72
- Aeras402
- Aeras485
- Anti-Wolbachia
- Shigella CP
- NRRV
- Pox Protein
- Dapivirine Ring
- NITD 609
- PCV (SII)
- HPV Vx
- RTS,s
- Leish F3
- Anti-Secretory
- Hookworm
- Bed Nets
- NID
- EDD
- TB
- Malaria
- Pneumonia
- HIV/AIDS
- Surgical Male Circumcision

Bubble size is equivalent to the amount of DALYs averted.
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
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
Scanning in TB patients show heterogeneous response within the lung.
PET IMAGINE COULD PROVIDE AN EARLY SIGNAL OF EFFICACY IN HOST DIRECTED THERAPY

Lesion at diaphragm shows differential labeling pattern
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 Confinement | X | X | X | X | X | X | X | +/− | X | X | X | X | X | X | X
Drug Rx | | | | | | | | | | | | | | | |
PK | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X
PCR | | | | | | | | | | | | | | | |

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

? Rescue Drug Rx
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

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

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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

**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

Notes:
1. Unless stated all challenges with C. parvum.
2. Work below the line may be considered later.
THE PROBLEM: WE HAVE A VAST PORTFOLIO OF IDEAS AND PROTOTYPES

PRECLINICAL Candidate Portfolio**

PHASE I 5 Vaccines 3 Drugs

PHASE II 12 Vaccines 5 Drugs

PHASE III 1 Vaccine 8 Drugs

REG / PQ 2 Vaccines 4 Drugs

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

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 III: DRUGS

BRV-LYO  DPV  d4T (20 mg)  TNF  Tafenoquine  DPzed  Fexinidazole  BPaL  PaMZ

REG/PQ: VACCINES

Euvichol  RTSS

REG/PQ: DRUGS

Generic DMPA  NES/EE combined vag ring  Sino-Implant  PAped

*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
OVERVIEW
SLIDE ON WHAT
THE CHALLENGE
MODEL IS?

CHALLENGE MODEL APPROACH

xxx

xxx

xxx

xxx

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

<table>
<thead>
<tr>
<th>xxx</th>
<th>xxx</th>
<th>xxx</th>
<th>xxx</th>
<th>xxx</th>
</tr>
</thead>
</table>

...
CONTROLLED HUMAN INFECTIONS MODELS (CHIMS) FOR ENTERIC VACCINES

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
**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

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**Days:** 0, 7, 21, 28, 42, 49, 62, 70, 77, 98, 180, 365

- **Vaccinate**
- **Serum**
- **PBMCs**

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

EDD from Evan
**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 (~$3 \times 10^9$ of each strain).
**INVENTORY / GAP ASSESSMENT**

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Strain</th>
<th>Shigella whole cell (WC Lead)</th>
<th>DB Fusion 6 (Sub Unit Backup)</th>
<th>GMMA 1</th>
<th>Truncated whole cell</th>
<th>WRSS1 (Live Att)</th>
<th>CVD1208S 3</th>
</tr>
</thead>
</table>
| S. flexneri 2a  
CHIM from Karen K at CVD | 2457 strain Frozen seed est., dose has been determined 8 | 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 |  |  |  | | | no |
| S. Sonnei 53G  
CHIM from Bob @ CCHMC Lyo | -53G Plate grown  
-53G Lyo (proposed) | 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 2018
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

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**Most useful**

**Somewhat useful**

**useful**

**Neutral**

**Not useful**

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## INVENTORY / GAP ASSESSMENT

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

<table>
<thead>
<tr>
<th>Model (Strain)</th>
<th>CHIM</th>
<th>Information Provided by Model</th>
<th>ETVAX ¹ (WC Lead Product)</th>
<th>FTA (SubUnit Candidate)</th>
<th>ST ⁵ (Bolt on)</th>
<th>dmLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>H10407 (CFA/1, LT,ST)</td>
<td>Pre-existing standard</td>
<td>Protection; role of dmLT, establish whether CS6 is a protective antigen</td>
<td>Would provide false positive protection results²</td>
<td>Applicable, but B7A has more utility for POC against CS6 component</td>
<td></td>
<td>We have ACE527 +/- dmLT data but haven’t parsed out the adjuvanticity vs antigen effect</td>
</tr>
<tr>
<td>E24377A² (LTST, CS1+CS3)</td>
<td>Development of strain already granted EVI3 = $ ____</td>
<td>Protection; contribution of anti-CS3 to protection,</td>
<td>Would establish protection against CS3 ETEC strain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B7A³ (ST,LT,CS6)</td>
<td>Development of strain and challenge regimen already granted EVI3 = $ ____ Plate grown</td>
<td>Protection with novel antigen; novel route of immunization; contribution of CS6 to protection</td>
<td>Would establish protection against CS6 ETEC strain</td>
<td>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 vaccination⁶</td>
<td></td>
<td>Has LT…same problem as above</td>
</tr>
<tr>
<td>-Plate grown refinement funded in EVI3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Lyo Prep proposed in CHIM (EVI) From Dick @EVI</td>
<td>CHIM proposal (Lyo B7A)= $ ____</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST TW10590 &amp; TW10681 From Wilbur Chen at CVD</td>
<td>EVI3 with DfdD = $ ____</td>
<td>First demonstration of Contribution of Strain-ST to protection, which could lead to its inclusion in many vaccines</td>
<td>Not applicable until point at which ETVAX and ST would be combined</td>
<td>Applicable, but B7A has will likely become our POC study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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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 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.

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Somewhat useful
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Neutral
Not useful