MALARIA VACCINES:
FROM PARASITES TO PREVENTION

Global Health:
Voices from the Vanguard
Lecture Series
University of Georgia
Athens, GA
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MALARIA

*P. falciparum* responsible for more deaths in children in the world than any other single infectious agent

Thousands of children will die today of malaria, an estimated million in the next year.
SANARIA’S PRIMARY MISSION

To develop, license, and deploy a vaccine based on attenuated *Plasmodium falciparum* sporozoites that reduces morbidity and mortality in infants and children in sub-Saharan Africa.
BEN KEAN
Course in Tropical Medicine
Second Year of Medical School
SUMMER FELLOWSHIP
COLOMBIA

Year Off in Colombia, Ecuador, Peru
Experience Tropical Medicine First Hand

Typhoid Fever – 10 days in the hospital
Amebic dysentery x 3
Giardiasis
Family Medicine Residency

Diploma in Tropical Medicine and Hygiene

LSHTM
JOIN THE NAVY!
THE JOY OF MAKING AN IMPACT
SEARCHING FOR A SHORTCUT TO A CURE
“Dad, check them for malaria.”
A VACCINE IS THE ANSWER

Need to Retool
RISKY BUSINESS-CRASH LANDING KENYA
THE ROAD TO SANARIA

• Develop subunit vaccine for malaria
  – Many clinical trials of PfCSP vaccine
    • Conclusion – Single protein vaccine not adequate for military personnel
  – Immunize with irradiated sporozoites
    • Identify targets and immune mechanisms
      – Better subunit vaccine
  – Sequence the genome of *P. falciparum*

• Join Celera Genomics

• Analyze irradiated sporozoite data
# IMMUNIZING BITES | # PROTECTED/ # CHALLENGED | # PROTECTED/ # CHALLENGES
---|---|---
> 1000 Immunizing Bites |  | 33/35
1\textsuperscript{st} challenge | 13/14 (93%) | 13/14 (93%)
Re-challenge <10 wk | 6/6 (100%) | 15/15 (100%)
Re-challenge 23-42 wk | 5/6 (83%) | 5/6 (83%)
<1000 Immunizing Bites |  | 5/15
INTERPRETATION

• Limited studies
  – 35 challenges in 14 people
• Protective immunity as good as protective immunity of any vaccine for any indication.

Hoffman et al. JID, 2002
WHY NOT PURSUED PREVIOUSLY?

• Technical limitations—not practical
• Discovery and cloning of perhaps “major” targets of attenuated sporozoite and naturally acquired immunity
  – Circumsporozoite protein (CSP) (1979)
  – Merozoite surface protein 1 (MSP1) and other asexual erythrocytic stage antigens (1981-1983)
• By 1984 a subunit *P. falciparum* CSP or asexual erythrocytic stage vaccine was “imminent.”
  • No need to pursue attenuated sporozoite vaccine
RATIONALE FOR STARTING SANARIA

• Immunogen reproducibly protects non-immunes for at least 10 months.
• Success based on bio-engineering, and applied entomology, parasitology, and biology.
  – Producing a vaccine in mosquitoes and controlling all elements of the production process
• Counsel of experienced, prominent individuals.
  – CBER
  – Merck Vaccine Institute
• Plan for paying for development and deployment in Africa.
  – Same vaccine for entire world
SANARIA’S APPROACH DIFFERENT

- Live attenuated whole organism
  - Other approaches subunit, recombinant
- Prevent infection in > 90% of recipients
  - Other current approaches are intended to reduce parasite burden by reducing rate of infection and/or replication of parasites, and thereby the pathological effects of the parasites.
WHY IS SANARIA WORKING ON AN ATTENUATED LIVE PARASITE VACCINE?

Why isn’t Sanaria working on a modern recombinant or synthetic vaccine?
INTENDED CHARACTERISTICS OF THE VACCINE

• Prevents infection by *P. falciparum* in greater than 90% of recipients,
  – For at least 6 months without additional exposure to sporozoites
  – Indefinitely with exposure to sporozoites
    • Re-immunization
    • Natural exposure to infected mosquitoes
THIS LEVEL OF PROTECTION HAS BEEN ACHIEVED WITH ATTENUATED SPOROZOITES IN HUMANS.

This level of protection has not been achieved by recombinant or synthetic vaccines in humans.
WHO WILL BE IMMUNIZED TO FULFILL OUR MISSION?

- **Infants in sub-Saharan Africa**
  - Approximately 25 million born annually
    - Directly reduce morbidity and mortality

- **Pre-adolescent and early adolescent girls**
  - New cohort of 7.5-10 million annually
    - Reduce fetal loss and morbidity and mortality in offspring

- **Travelers from non-endemic countries to endemic countries**
  - 100 million such travelers annually
    - Protect travelers
    - Provide funds to drive optimal deployment of vaccine to the other two populations

- **Others**
  - Many other populations in Africa, Asia, Oceania, and the Americas
    - Mass Administration?
LIFE CYCLE OF PLASMODIUM
SANARIA PfSPZ VACCINE: PROGRESS

- Research & Development
- Process Development
- Manufacture - cGMP
- Clinical Trials
RESEARCH AND DEVELOPMENT
CRITICAL R&D QUESTIONS

• Can one administer the attenuated sporozoites by a route that is practical for a vaccine?
  – Yes

• Can one produce adequate quantities of sporozoites?
  – Yes

• Can one at a reasonable cost produce attenuated PfSPZ that meet regulatory requirements to be a vaccine?
  – Yes
MAJOR CHARACTERISTICS OF SPOROZOITES REQUIRED TO MEET REGULATORY REQUIREMENTS

- Free of pathogens
  - Standard FDA-mandated assays
- Free of significant amounts of mosquito salivary gland material
  - Salivary gland material assay
- Adequately attenuated
  - Physical and biological assays
- Potent (cryopreserved)
  - Potency assay
PROCESS DEVELOPMENT
PROCESS DEVELOPMENT

- Integrated campaigns
  - 7 performed in 2006
- Production campaigns (engineering/shakedown)
  - 5 performed in 2006
MANUFACTURING UNDER CURRENT GOOD MANUFACTURING PRACTICES (CGMPs)
GMP PRODUCTION CAMPAIGNS FOR TOXICOLOGY LOTS

- Release assays
- Stability studies
- Toxicology studies
- Retention

REQUIRES A TOTAL OF 228 VIALS
PRODUCTION CAMPAIGNS 7-10
Toxicology Lots

<table>
<thead>
<tr>
<th></th>
<th>Production</th>
<th>Campaign</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Mosquitoes dissected</td>
<td>2201</td>
<td>1509</td>
<td>2146</td>
</tr>
<tr>
<td>Number of vials produced</td>
<td>301</td>
<td>281</td>
<td>360</td>
</tr>
</tbody>
</table>
PRODUCTION CAMPAIGNS 7-10

- In Process Assays
- Release Assays
  - Vaccine Bulk Product
  - Vaccine Final Product (in vial)
- Stability Assays on Vaccine Final Product
RABBIT REPEAT DOSE TOXICOLOGY STUDIES

safe and non-toxic
INDIVIDUAL SERA PfCSP ELISA/PfSPZ IFA 2 weeks after 4th dose

<table>
<thead>
<tr>
<th>PfSPZ Vaccine Immunization group</th>
<th>PfCSP ELISA Geometric Mean OD 1.0 N=24</th>
<th>PfSPZ IFA Geometric Mean Titer N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>5,131</td>
<td>3,200</td>
</tr>
<tr>
<td>ID</td>
<td>55,805</td>
<td>51,200</td>
</tr>
</tbody>
</table>
BIODISTRIBUTION STUDIES

no unexpected results
Team working at ‘dismal strip mall...’ National Geographic, July 2007
SANARIA’S NEW FACILITIES
NEW FACILITIES PHYSICAL PLANT GRAND OPENING 10/26/2007

We celebrated the perfect end to an early chapter in the story of the fulfillment of our mission!
NEW FACILITIES PHYSICAL PLANT

11/28/2007
Shakedown production campaign.
PRODUCTION CAMPAIGNS 20-25
“PfSPZ Vaccine Clinical Lots”
EACH PC DESIGNED TO PRODUCE AT LEAST ENOUGH VIALS FOR

• Release Assays
• Retention Samples
• Stability Assays
• The first clinical trial – 100 volunteers
## PRODUCTION CAMPAIGNS 20-25

<table>
<thead>
<tr>
<th>Production Campaign Number</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>Mean</th>
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<tbody>
<tr>
<td><strong>Mosquitoes dissected</strong></td>
<td>2997</td>
<td>2997</td>
<td>2244</td>
<td>3173</td>
<td>2655</td>
<td>2727</td>
<td>2799</td>
</tr>
<tr>
<td><strong>Pf Sporozoites/Mosquito</strong></td>
<td>62,774</td>
<td>84,492</td>
<td>64,390</td>
<td>74,107</td>
<td>79,065</td>
<td>61,508</td>
<td>71,056</td>
</tr>
<tr>
<td><strong>Number of vials produced</strong></td>
<td>474</td>
<td>576</td>
<td>476</td>
<td>718</td>
<td>632</td>
<td>543</td>
<td>570</td>
</tr>
</tbody>
</table>
CONTROL ASSAYS

- In-process
- Vaccine Bulk Product
- Vaccine Final Product
# SUMMARY OF PRODUCTION CAMPAIGNS 20-25: IN-PROCESS ASSAYS

<table>
<thead>
<tr>
<th>Production Campaign Number</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disinfected Eggs Bioburden USP&lt;61&gt;</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Pupae used Bioburden USP&lt;61&gt;</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Pf gametocyte infected blood meal Bioburden USP&lt;61&gt;</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Pf infected mosquitoes used (≥ Bioburden USP&lt;61&gt;</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Alanine dosimetry beads</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
</tbody>
</table>
### SUMMARY OF PRODUCTION CAMPAIGNS 20-25: RELEASE ASSAYS FOR VACCINE FINAL PRODUCT

<table>
<thead>
<tr>
<th>Production Campaign Number</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality – visual appearance,</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>pH</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Identity – reactivity in IFAT with MAb against PfCSP</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Quantity of sporozoites/vial</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Safety - Sterility USP &lt;71&gt;</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Safety - Bacterial endotoxin</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td>Safety - 6-Day Hepatocyte Attenuation Assay</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
</tbody>
</table>
STABILITY STUDIES
**STABILITY OF PRODUCTION CAMPAIGN 2**
*(Vialed, 7/5/06)*

<table>
<thead>
<tr>
<th>DATE OF TESTING (Months after Vialing)</th>
<th>July 2006 (0 m)</th>
<th>January 2007 (6 m)</th>
<th>May-June 2007 (10.5-11.5 m)</th>
<th>Dec-Jan 2008 (18 m)</th>
<th>June 2008 (24 m)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality – visual</strong></td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
</tr>
<tr>
<td><strong>Quantity of sporozoites/vial</strong></td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Potency – 3-Day Hepatocyte Assay</strong></td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>Pass</td>
<td>91%</td>
</tr>
<tr>
<td><strong>Sporozoite Viability Assay</strong></td>
<td>FIO</td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>
STABILITY OF PC 9 AND PC 10 “Toxicology Lots”

At 18 Months Stable and Sterile (> 11%)
IND
PHASE I TRIAL WITH CHALLENGE – U.S.
CLINICAL TEAM

U.S. Military Malaria Vaccine Program

University of Maryland Center for Vaccine Development
A Phase 1 Trial with Challenge of The PfSPZ Vaccine Administered Subcutaneously or Intradermally to Malaria-Naïve Adult Volunteers
GROUPS 1 – 4 (SC and ID)

Dose 1 2 3 4

7 SC 7 ID
7,500 SPZ/dose

11 SC 11 ID
30,000 SPZ/dose

11 SC 11 ID
135,000 SPZ/dose

11 SC 11 ID
135,000 SPZ/dose

3 months

5 6
<table>
<thead>
<tr>
<th>Group</th>
<th># Volunteers Immunized</th>
<th>Route</th>
<th># SPZ per injection</th>
<th># Doses</th>
<th># Infectivity Controls</th>
<th>Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>SC</td>
<td>7.5 K</td>
<td>4</td>
<td>6</td>
<td>3 Wks post 4th dose</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>ID</td>
<td>7.5 K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>SC</td>
<td>30 K</td>
<td>4</td>
<td>6</td>
<td>3 Wks post 4th dose</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>ID</td>
<td>30 K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>SC</td>
<td>135 K</td>
<td>4</td>
<td>6</td>
<td>3 Wks post 4th dose</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>ID</td>
<td>135 K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>SC</td>
<td>135 K</td>
<td>4 or 6</td>
<td>6</td>
<td>3 Wks post 6th dose</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>ID</td>
<td>135 K</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TIMELINE

2008  2009

December  January  Feb  April/ May  Aug/Sept

SECNAV Designee Approval

- Final protocol approved by all IRBs (UMD will wait for IND #)
  - Submit IND

Start recruitment

First immunizations

First protection data
IMMUNOLOGY STUDIES

• Antibodies
  – ELISA (Protein Potential/WRAIR)
    • PfCSP, PfLSA-1, PfMSP-1, PfEBA-175
  – IFA (Protein Potential)
    • Sporozoites, Liver stages, Asexual and sexual erythrocytic stages

• T cell studies (whole sporozoites)
  – ELIspot (NMRC)
  – Intracellular cytokine staining (VRC, NIAID)
SOME CLINICAL VACCINOLOGY QUESTIONS

- Dose
- Number of doses
- Interval between doses
- Volume of each dose
- Number of sites for each dose
- Route of administration
- Longevity of protection without any exposure
- Boosting of protection by exposure to sporozoites
- Protection against heterologous challenge
- PROTECTION AGAINST *P. vivax*!!
CLINICAL DEVELOPMENT PLAN

How do we achieve a successful BLA and commercialization ASAP?
CLINICAL DEVELOPMENT PLAN – EXPERIMENTAL CHALLENGE

U.S. (USMMVP, U of MD CVD, others?)
Europe (RUNMC, others?)
Colombia (Instit of Immunol)
CLINICAL DEVELOPMENT PLAN – FIELD STUDIES

1st Step-Africa
U of MD CVD, NIAID,
Noguchi-Ghana
SITE VISIT TEAM

- MVI (Laurence Lemiale)
- CVD (Matt Laurens, Chris Plowe)
- MCTA (Bernhards Ogutu)
- NAMRU-3 Ghana (Karl Kronmann)

- Sponsored by MVI, Navy, MCTA, HHMI
Site visits
September 2008
HOW DO WE GET THE PfSPZ VACCINE THERE?
GOALS:

1. Demonstrate PfSPZ vaccine transport through a below -140°C cold chain from Sanaria to the clinical trials site at Navrongo.

2. Determine infrastructure and LN2 availability at Noguchi Memorial Institute and Navrongo; determine needs for receiving, storing and handling vaccine for a clinical trial.

OUTCOMES:

1. PfSPZ vaccine samples travelled 14,500 miles. Viability assay indicated no change in spz viability.

2. 3 sources of LN2 are available. Hub (Noguchi) and spoke (Navrongo) distribution feasible. Needed upgrades identified.
WHERE ARE WE GOING WITH THE MANUFACTURING PROCESS AND CONTROL ASSAYS?

Optimize Efficiency
Scale-Up
Validate

Required for Design of Facility for Manufacturing PfSPZ Vaccine for Pivotal Phase III Studies and Commercial Launch
RESEARCH

• Parasites
• Mosquitoes
• Extraction
• Formulation
• Thermostabilization
• Logistics
• Administration
LIFE CYCLE OF PLASMODIUM
MALARIA VACCINES IN THE TRANSITION
FROM SCALE-UP TO ERADICATION

Vaccines that reduce morbidity and
mortality without preventing transmission

Scale up
Coverage

Disease and
Transmission
Elimination

Eradication

Vaccines that prevent transmission by preventing blood stage
infection and/or productive gametocyte infection of mosquitoes
HOW GOOD IS GOOD ENOUGH?
COLLABORATIONS and PARTNERSHIPS

- PATH Malaria Vaccine Initiative
- Protein Potential LLC
- US Military Malaria Vaccine Program
- National Institute of Standards & Technology (NIST)
- University of Maryland, Center for Vaccine Development
- University of Maryland Biotechnology Institute
- Radboud University Medical Center of Nijmegen
- University of Leiden
- Columbia University
- JC Venter Institute
- NIAID Laboratory of Malaria and Vector Research
- NIAID Department of Microbiology and Infectious Diseases
- Centers for Disease Control (Malaria Epidemiology)
- Transform
- MIT
- Harvard
- Noguchi Memorial Institute of Medical Research
- Navrongo Health Research Center
- Manhica CISM
- Nanopass, Pharmajet
FUNDING

• NIAID (SBIR Program)
• USAMRMC
• Institute for OneWorld Health
• PATH-Malaria Vaccine Initiative
• Top Institute Pharma (TI Pharma)
• BMGF
ACKNOWLEDGEMENTS

• ADVISORY COMMITTEE
• EAC – SAFETY
• CLINICAL VACCINOLOGY ADVISORY GROUP