The NIH Pre-Clinical Pipeline: The Role of the IPCP-HTM Program in Clinical Advancement of Candidates

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What is Really Needed to Advance a Microbicide to Clinical Testing?

Conceptual Microbicide Pipeline

R&D

In vitro Validation

Virology
Pharmacology
Toxicology
Preclinical Studies

Clinical Testing
SAFETY

Clinical Testing
EFFICACY

Marketing
& Distribution
Phase IV Studies

Marketing
OTC Product

Consumer

Pre formulation & Formulation

Chemistry, Manufacturing and Controls (CMC)

Behavior: Acceptability & Use

Federal, Local and State Regulations
Product Specific
FDA requirements
A little Closer look!

Preclinical

General Preclinical
- Virology
  - Antiviral activity
  - Toxicity Cell lines/Primary cells
  - Range of Action--Subtypes
  - Mechanism of Action
  - Resistance
  - Combination
  - Relevant Matrices

Petri dish

Microbiology Specific
Lab
- Condom Compatibility
- Effect on Lactobacilli
- Effect of Matrices
  - Seminal Plasma
  - Cervical fluid
  - Mucin
- Other STIs
- Cervical Explants
- Murine, NHP safety and efficacy

Animal
- 10-14 day Rabbit Vaginal Irritation (RVI)
- Systemic Absorption by iVag
- Penile Irritation

PK and Toxicology

Systemic Absorbance following iVag admin.

Yes
- iVag AND systemic

No
- iVag, +/- Systemic

- Maximum tolerated dose (MTD)
- Acute Toxicity
- Chronic Toxicity, 90+ days
- PK and Metabolites (ADME)
- General Genotoxicity
- Carcinogenesis
- Reproductive toxicology
  - Seg. I Reproductive performance
  - Seg. II Teratology
  - Seg. III Perinatal/Post natal
- Dermal/systemic Hypersensitivity
- Dermal/systemic Photosensitivity

Preformulation
- Stability
- Sterility
- Homogeneity
- Purity

Formulation
- Stability
- Sterility
- Homogeneity
- Purity

Chemistry Manufacturing and Control (CMC)
- Unformulated Drug Product
- Formulated gel
- Stability, Sterility, Packaging, Storage

Applicator
- Selection Labeling
- Acceptability Filling
We Have More Questions Than Answers

What is required to identify a safe, efficacious and acceptable microbicide in the absence of the “proof-of-concept” in humans that a microbicide can prevent HIV transmission?

1. How do we measure safety, efficacy and acceptability?
   - Biomarkers
   - Acceptability tools
   - Tools to measure microbicides impact on the mucosal environment

2. What are the requirements for “protection”
   - Distribution
   - Microbicide properties

3. When do we need the microbicide—Coital, Pericoital, sustained protection
How is NIAID Addressing These Many Issues?

Targeted funding to:

- Support the preclinical development of promising candidates
- Support transition of candidates through critical path/preclinical development to create IND-enabled clinical candidates
- Support the development of basic and preclinical science required to enable microbicide development and clinical trials
Tools For Microbicide Development

Microbicide Innovation Program (MIP)

Integrated Preclinical Clinical Program For HIV Topical Microbicides (IPCP-HTM)

Microbicide Trials Network

Each Component Serves a Function

Microbicide Innovation Program (MIP)  “Engine for Innovation”

IPCP-HTM : “Engine for Development” = Mini-Pipelines

MTN:  “Engine for licensure”

Contracts:  Sponsor Assistance Mechanism --Gap-filling

Integration of Components = Microbicide Pipeline
Why have the IPCP-HTM?

Enabling a microbicide for clinical testing requires meeting FDA and/or other regulatory agency (European, country specific), requirements are a complex and costly activity---Must minimally:

• Establish toxicology and pharmacology in animal models
• Ensure purity and stability of the Microbicide and its delivery system

Burdened by the fact that most of our tools to enable clinical testing must be adapted from oral or systemic drug requirements

The microbicide field is rapidly evolving and thus needs:

• New candidates
• Delivery systems ---Rings and films
• Technologies to:
  • Address safety issues as they arise
  • More efficiently select candidates for clinical testing
  • Study new delivery systems as they are developed:
    • Rings
    • Films
    • Novel gels ---smart gels, nano-gels
**The Integrated Preclinical Clinical Program for HIV Topical Microbicides (IPCP-HTM)**

**The Nutshell View**

Multi-Project and -Core grant that requires an industry partner. IPCP-HTM program may include Pre-phase 1 clinical trials

First awards in 2001—continuous (except for 2007)

- 27 awards
- >200 investigators involved
- >100 Peer reviewed publications
- >500 Presentations and abstracts at more than 20 national and international conferences, including CROI, Microbicides and IAS
- Developed Gels, Films and Intra-vaginal rings
- Has conducted 31 clinical trials

*Small (Pre-Phase 1) trials designed to prioritize candidates or address pertinent scientific questions that advance microbicide clinical science*
**IPCP-HTM Program: 2010**

**Overarching Objective: Support the Microbicide Pipeline**

Currently 11 Awards in the IPCP-HTM Program

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<th>Inhibitors</th>
<th>Delivery Strategies</th>
<th>Approaches</th>
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<td>1. Entry inhibitors</td>
<td>1. Combination</td>
<td>1. Vaginal</td>
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<td>❖ Small molecule</td>
<td>2. Coital/non-Coital</td>
<td>2. Rectal</td>
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<tr>
<td>❖ Large molecule</td>
<td>❖ Gel</td>
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<tr>
<td>2. ART-based</td>
<td>❖ Ring</td>
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<td>3. Alternative strategies</td>
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<td>❖ Oligomers</td>
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The IPCP-HTM
Contributions to the
Clinical Pipeline
Select a “Best” formulation

Formulations
- Rheological Properties
  - Viscosity
  - pH
  - Etc.
- Preformulation
- Stability
- Formulation

Virology
- Activity in:
  - Primary cells
  - Explants
  - Etc.

Clinical Trials
- Vaginal/GI spread
  - Sitting, standing, simulated coitus
- Semen simulant and virus surrogate
- Effect in Uterus

Other Clinical Trials
- New methods for detection of gels
- Optimizing detection methods
- Imaging to model GI or vaginal events

Optimal Gel for a Clinical Trial

Biosyn, Inc.: U19 AI051650
Anton: U19 AI060615
McGowan: U19 AI082637
New Safety Measures

In Vivo Tissue Imaging
Develop scoring system

Clinical Trial
Evaluation of Optical Coherence Tomography (OCT) as a Safety Tool for Assessment of Vaginal Products
Women N=18
5.5 days 2 x day Conceptrol: Placebo
OCT pre-, last gel use and 7 days post
Acceptability and impact of OCT

Rambouillet sheep

Starpharma Ltd. U19 AI060598
Effect of Semen/Ejaculate on Microbicide Activity

IN VITRO

Anti-HIV Activity of PRO 2000

PRO 2000 dose mcg/ml

IN VIVO

Clinical Trial
0.5% PRO2000, N=24, Measure vaginal response to PRO2000

No proinflammatory response
Decrease in hBD2, SLPI, IL-1RA, IgA

Does PRO2000 lose activity in vivo following sexual intercourse?

N=10 couples

Control
Intrinsic
Coitus
PRO2000
Coitus+ PRO2000

Loss of Intrinsic activity
Loss of PRO2000 activity

Herold U19 AI077549
Keller U19 AI069551

Keller et al. AIDS 2007, 21:467
Can Formulation Properties be Correlated with Acceptability?

Formulation
- Viscosity
- Osmolarity
- Shearing
- Stickiness
- Mixing/miscibility
- Color
- Spreading
- Coating
- Adhesion to surfaces

Acceptability
- Gels and Rings
  - Leakage
  - moisture
  - Sexual pleasure
  - Sexual comfort
  - Removal & disposal
  - Long residence
  - Application

Link Biophysical with Women’s perception

Focus group in mano
Clinical experience

Identify specific formulation characteristic that yield specific women responses

Develop new tools to measure topical microbicide acceptability

DHHS/NIH/NIAID/DAIDS/PSP

Buckheit U19 AI077289
Rectal Microbicide Program

Behavioral

- Anal Health and Behavior Survey
  - Signs and Symptoms
  - Acceptability
    - Delivery format:
      - Enema
      - Suppository
      - Applicator

Formulation /PK/PD

- Distribution
  - Simulated Coitus
  - Semen and Virus Surrogates
- Enemas
  - Safety
- Vehicles
  - Aqueous and Lipid Formulations
    - Dose Form

Safety

- UC781
  - First rectal use of vaginal formulation
  - Biopsy Challenge
- RMP-02/MTN006
  - TNV oral and rectal gel

Rectal Specific Formulations
- Tenofovir, UC781, Combination
Rectal Microbicides

Microbicide Development Program
- Behavioral component
- Signs symptoms delivery format
- Formulation and deployment
- Osmolarity gel type
- Rectal use of Vaginal gels
  - UC781 (RMP01)
  - Tenofovir (RMP02/MTN006)

Safety
- Acceptability
- Trial Methods
- Surrogate markers

Combination HIV antiviral Rectal Microbicide program (CHARM)
- Rectal specific Formulation
  - Tenofovir
  - UC781
  - Combination

MTN007 Rectal 1% TNV gel

Anton U19 AI060615, McGowan U19 AI082637
RMP-002/ MTN-006-A Unique Hybrid Trial by the MTN and the IPCP-HTM Program

**Dosing**
- Single oral dose of tenofovir
- Single rectal dose of tenofovir
- 7 daily doses of tenofovir

**Analysis**
- Ex Vivo Biopsy
- Infection

**Pharmacokinetics** *(oral and rectal dosing)*
- Plasma
- PBMC
- Rectal Fluid
- Rectal Tissue
- Vaginal fluid

**Safety**
1. General
2. Mucosal

**Courtesy of Ian McGowan**
IPCP-HTM and Rectal Microbicides
Creation of a pipeline

Preclinical Development
In vitro assays → Explants → NHP/BLT mice

Formulation and Deployment

Study 1 (N=9)
Hyper- iso- and hypo-osmolar
Acceptability, PK and safety (cytokines, explant challenge, permeability)

Study 2a (N=8)
Distribution of Possible Rectal gels
Water soluble
Lipid Soluble

Study 2b
Autologous semen
Simulated coitus

Behavior and Acceptability

Study 1
+/− RAI, HIV+, HIV- n=448 ♀, ♂
STI, RAI Symptoms, Anoscopy
Self-report Behaviors

Study 2
+/− RAI, HIV+, HIV- n=80 ♀, ♂
Rectal Microbicide Acceptability
OTC: Gel, foam, gel applicator, suppository, enema

Candidate selection
Optimal distribution and gel characteristics
Factors
Impacting potential Rectal microbicide use

DHHS/NIH/NIAID/DAIDS/PSP
Wrap-Up

The IPCP–HTM has provided support for exploratory studies that are helping to:

1. Select candidates
2. Understand the interaction of microbicides with genital mucosa
3. Develop new approaches to measure safety, efficacy and acceptability
4. Creating a rectal microbicide pipeline