Overview of Non RT-Microbicides

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David Geffen School of Medicine
Los Angeles
Overview

• Classification and mechanism of action of non-RT microbicides
• Non-RT microbicides
  – SPL7013 (VivaGel™)
  – Carraguard
  – Cellulose acetate phthalate (CAP)
• Innovative formulations
• The MTN pipeline
viral disruption

prevention of STDs

maintenance of normal microflora

Gel/cream:
- physical barrier
- lubrication

inhibition of HIV uptake by dendritic cells (e.g. anti-DC-SIGN)

inhibition of reverse transcriptase

fusion/absorption inhibition (e.g. polyanions, co-receptor antagonists)

McGowan Biologicals 2006
Adapted from Shattock and Moore, Nat Rev Microbiol, 2003
# Microbicide Pipeline

<table>
<thead>
<tr>
<th></th>
<th>Pre-Clinical</th>
<th>Safety</th>
<th>Efficacy</th>
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<td>Pro2000, Carraguard, Buffergel</td>
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<td><strong>NRTI &amp; NNRTI</strong></td>
<td>DABO</td>
<td>PMPA, UC-781, TMC-120, MIV-150</td>
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<td><strong>Membrane active</strong></td>
<td></td>
<td>SLS</td>
<td></td>
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<td><strong>Unclassified</strong></td>
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<td></td>
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</tr>
<tr>
<td><strong>Combination</strong></td>
<td>PC-815, Truvada, NRTI/NNRTI, NRTI/P, NNRTI/P</td>
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SPL7013

(VivaGel™)
SPL7013 (VivaGel™)
SPL7013 (VivaGel™)

• Polylysine dendrimer molecule with 32 copies of naphthalene-3, 6-disulfonate
• In vitro activity against HSV-2 and HIV-1
• INDs filed for both indications
• Completed Phase 1 study (0.5% - 3% w/w SPL7013) seven doses
• Ongoing Phase 1 study under STI-CTG auspices in San Francisco and Kisumu, Kenya
• Phase 1 rectal safety study in planning stage
MTN-004

- Phase 1, double blind, randomized, controlled comparison with 14 days of twice daily exposure to 3% w/w SPL7103 Gel or placebo gel in HIV-uninfected sexually active women

<table>
<thead>
<tr>
<th>Arm</th>
<th>Description</th>
<th>N</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>SPL7013 Gel</td>
<td>20</td>
<td>BID (14 days)</td>
</tr>
<tr>
<td>2</td>
<td>Placebo Gel</td>
<td>20</td>
<td>BID (14 days)</td>
</tr>
</tbody>
</table>
Primary Objective

• To assess the safety of 3% w/w SPL7013 Gel when administered for 14 consecutive days on the vulvar and cervicovaginal mucosa of healthy sexually active HIV-negative women aged 18-24 years
Secondary Objectives

• To assess the **adherence** to a short-term regimen of 3% w/w SPL7013 Gel among healthy sexually-active HIV-negative women aged 18-24 years

• To evaluate product **acceptability** among healthy sexually-active HIV-negative women aged 18-24 years

• To assess the effect of a twice daily short-term regimen of 3% w/w SPL7013 Gel on the **vaginal microflora** of healthy sexually-active HIV-negative women aged 18-24 years
Exploratory Objectives

• Determine the pattern of cytokine/chemokine, innate immune factor changes, and functional activity associated with use of 3% w/w SPL7013 Gel in the lower reproductive tract of healthy sexually active HIV-negative women aged 18 – 24 years.

• Determine by means of dye-based applicator test the number of applicators returned to the study site that have been exposed to the vagina

• Determine the extent of SPL7013 absorption into the blood following the completion of product dosing
Primary Endpoints

- Abnormal genital symptoms judged by the Investigator to be possibly, probably, or definitely related to product use
- Abnormal pelvic exam findings, including colposcopic findings, judged by the Investigator to be possibly, probably, or definitely related to product use
- Grade 3 or higher laboratory values (as defined by the DAIDS Toxicity Tables) for hematology, liver function, creatinine level and coagulation judged by the Investigator to be possibly, probably, or definitely related to product use
- Adverse experiences judged by the Investigator to be possibly, probably, or definitely related to product use
## MTN-004 Study Design

<table>
<thead>
<tr>
<th>Activity</th>
<th>Screen 1</th>
<th>Screen 2</th>
<th>Enroll</th>
<th>Phone Call (D2)</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Screening</td>
<td>X</td>
<td>(X)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety bloods</td>
<td>X</td>
<td>(X)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
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<td>Pelvic exam</td>
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<tr>
<td>PK</td>
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<td></td>
<td>X</td>
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<tr>
<td>Behavioral</td>
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<td></td>
<td>X</td>
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<tr>
<td>Vag culture</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Innate factors</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
MTN-004 Sites

Student Health Center
University of South Florida
Tampa, Florida
**Site PI:** Diane Straub MD MPH

Maternal Infant Study Center (CEMI)
University of Puerto Rico
Medical Science Campus
San Juan, Puerto Rico
**Site PI:** Irma Febo MD
Innovative Aspects of MTN-004

• Collaboration between
  – DAIDS & NICHD
  – MTN & ATN

• Behavioral Sub study
  – Web based assessments
  – Daily cell phone driven questionnaires

• Innate immunity assessment
  – Cervical cytokines
  – Innate immune factors (SLPI and lactoferrin)
  – Functional activity (antibacterial and antiviral)

• Adherence assessment
  – Applicator dye test
# MTN-004 Timelines

<table>
<thead>
<tr>
<th>Activity</th>
<th>Due Date</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>Protocol development</td>
<td>November 2006</td>
<td>Completed</td>
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<tr>
<td>PSRC Review</td>
<td>December 2006</td>
<td>Completed</td>
</tr>
<tr>
<td>Response to PSRC</td>
<td>December 2006</td>
<td>Completed</td>
</tr>
<tr>
<td>Protocol sign off by DAIDS MO</td>
<td>December 2006</td>
<td>Completed</td>
</tr>
<tr>
<td>IRB Submission</td>
<td>January 2007</td>
<td>Completed</td>
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<tr>
<td>Protocol Registration</td>
<td>May 2007</td>
<td>Pending</td>
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<tr>
<td>Screening and enrollment</td>
<td>June 2007</td>
<td>Pending</td>
</tr>
<tr>
<td>Study completion</td>
<td>December 2007</td>
<td>Pending</td>
</tr>
</tbody>
</table>
Carraguard
Carraguard

- Sulfated polysaccharides extracted from seaweed.
- Used as gelling agents in cosmetics, lubricants, and the food industry, and are classified as GRAS by the FDA
- Inhibit HIV-1 transmission by binding to the HIV-1 envelope.
- Block cell trafficking of macrophages from the vaginal compartment
- A Phase 3 study has recently completed enrollment
- Combination product in development (Carraguard + MIV-150)
Cellulose Acetate Phthalate
Cellulose Acetate Phthalate

- Identified as a candidate microbicide through an excipient-screening program designed to identify compounds with anti-HIV-1 activity
- An anionic polymer belonging to the polycarboxylate group
- CAP works through blocking gp120 binding and induction of “dead-end” gp41 six-helix bundle formation
- A Phase 1 protocol is currently in development.
Formulation Innovations
New Formulations

• First generation of formulations were not optimized for vaginal or rectal use

• 2\textsuperscript{nd} generation products being developed on the basis of:
  – Stability
  – Rheological properties
  – Absorption
  – Local environment (rectum vs. vagina)
  – Acceptability

• Broader range of delivery systems
  – Gels, foams, films, suppositories, and rings
Imaging Where the Product Goes

Charles Lacey MD, & Craig Hendrix MD
TMC120 Vaginal Rings

Malcolm et al., Journal of Antimicrobial Chemotherapy, 2005
Rectal Microbicides
# Prevalence of Anal Receptive Sex

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Prevalence of AI</th>
<th>Reference</th>
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<tbody>
<tr>
<td>MSM in EXPLORE study</td>
<td>4295</td>
<td>48 – 54%</td>
<td>Koblin et al. 2003</td>
</tr>
<tr>
<td>High risk women</td>
<td>1268</td>
<td>32%</td>
<td>Gross M et al. 2000</td>
</tr>
<tr>
<td>College students</td>
<td>210</td>
<td>20%</td>
<td>Civic D 2000</td>
</tr>
<tr>
<td><strong>US Survey 15 – 44 years NSFG</strong></td>
<td>12,571</td>
<td>35-40%</td>
<td>Mosher WD et al. 2005</td>
</tr>
<tr>
<td>Californian residents</td>
<td>3545</td>
<td>6-8%</td>
<td>Erickson PI et al. 1995</td>
</tr>
</tbody>
</table>
## Women and RAI Outside the US

<table>
<thead>
<tr>
<th>Country</th>
<th>Ever Experienced RAI (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>31.0</td>
<td>Guimares MD et al. 1995</td>
</tr>
<tr>
<td>Peru</td>
<td>12.0</td>
<td>Caceres C et al. 1997</td>
</tr>
<tr>
<td>South Africa</td>
<td>42.8</td>
<td>Karim SS and Ramjee G 1998</td>
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<tr>
<td>Kenya</td>
<td>40.8</td>
<td>Schwandt M et al. 2006</td>
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</table>
Rectosigmoid Anatomy
Rectal Safety Assessment

Vaginal Microbicide
UC-781

Rectal Microbicide
(Product X)

Combination Microbicide
(Tenofovir)

Animal Toxicology

Phase 1 Rectal Safety

- Preclinical Evaluation
  - Cell lines
  - Explant studies
  - Animal models
  - Animal toxicology

- Human studies
  - Phase 1
  - Phase 2
  - Phase 2B/3
Design of UC-781 Phase 1 Rectal Safety Study

• Three arms (Men and women with history of RAI)
  – 0.1% UC-781 (N = 12)
  – 0.25% UC-781 (N = 12)
  – Placebo (N = 12)

• Single dose followed by 7 days of study drug
Design of UC-781 Phase 1 Rectal Safety Study

- **Primary objective:** To evaluate the safety and acceptability of 0.1% and 0.25% UC-781 vaginal microbicide gel versus placebo when applied rectally

- **Endpoints:**
  - Frequency of ≥Grade 2 adverse events
  - Acceptability
UC-781 Trial Design

Randomization: 0.1% UC-781, 0.25% UC-781, or placebo

Visit 1: Screening
Visit 2: Baseline
Visit 3: Single-dose Clinical Eval
Visit 4: 7 Daily doses Clinical Eval
Visit 5: Outpatient Phone interview

Flex <4 wk → ≥ 1 wk
Flex ≥ 1 wk
Flex ~ 8 days
UC-781 Phase 1 Rectal Safety Study

• **Secondary Objective:** To determine whether use of study product is associated with rectal mucosal damage

• **Endpoints:**
  – Epithelial sloughing
  – Histopathology
  – Mucosal mononuclear cell phenotype
  – Mucosal cytokine mRNA
  – Mucosal immunoglobulins
  – Fecal calprotectin
  – Explants- Mucosal cytokine mRNA and susceptibility to HIV infection
Applicator Design

Courtesy of Dr. Alex Carballo-Diequez/amfAR
The Rectal Phase 1 Pipeline
## Phase 1RM Safety Studies

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
<th>Timeline</th>
<th>Sponsor</th>
</tr>
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<tbody>
<tr>
<td>UC-781</td>
<td>Ongoing</td>
<td></td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>TBN</td>
<td>Planned</td>
<td>Q3 2007</td>
<td>NIAID/DMID</td>
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<tr>
<td>PRO-2000</td>
<td>Planned</td>
<td>Q1 2008</td>
<td>MDP MRC-UK</td>
</tr>
<tr>
<td>UC-781 (Rectal formulation)</td>
<td>Possible</td>
<td>Q4 2010</td>
<td>TBD</td>
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</table>
Bargello Museum, Florence, Italy
The MTN Pipeline
Requirements for MTN Assessment

New Microbicide Candidate

- IND Submitted
- Product available
- Product stability
- Investigational Brochure
Concept Development and Approval Process

New Microbicide Candidate
IND Submitted
Product available
Product stability
Investigational Brochure

Request comparative data
From MTN Central Lab

Science Committee
Product Selection Committee
Ethics Review

Financial Estimates & Site Interest

Protocol Concept

Concept Declined
Concept Review by EC
Protocol Development Triggered
What Products Might be Realistically Useful to MTN?

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<th>Phase 2B</th>
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<td>CAP</td>
<td>VivaGel™</td>
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<tr>
<td>RTI</td>
<td>GSK-248</td>
<td></td>
<td>UC-781 TMC-120</td>
<td>Tenofovir</td>
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<tr>
<td>Integrase</td>
<td>GSK-364735</td>
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<tr>
<td>CCR5</td>
<td>RANTES analogues</td>
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Summary
# The Microbicide Pipeline in 2007

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<tr>
<th>Category</th>
<th>Preclinical</th>
<th>Animal models</th>
<th>Cost</th>
<th>Major hurdles</th>
<th>Efficacy trials</th>
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<tr>
<td>Polyanions</td>
<td>Virucidal X4</td>
<td>Data for X4 only</td>
<td>Cheap</td>
<td>Coitally dependant</td>
<td>Started</td>
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<tr>
<td></td>
<td>Blockade R5</td>
<td></td>
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</tr>
<tr>
<td>ARVs</td>
<td>Activity for X4 &amp; R5 (prolonged)</td>
<td>Data for PMPA</td>
<td>Affordable</td>
<td>Resistance</td>
<td>1-2y</td>
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<tr>
<td>Small molecule inhibitors</td>
<td>Potent, but Specific X4/R5</td>
<td>Data for CMPD167 &amp; BMS806</td>
<td>Affordable</td>
<td>Coitally dependant</td>
<td>2-3y</td>
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<tr>
<td>Proteins</td>
<td>Active in nm range</td>
<td>Data for b12, CV-N, PSC-RANTES</td>
<td>Expensive</td>
<td>Production</td>
<td>?</td>
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<tr>
<td>Peptides</td>
<td>Target gp120 Co-receptors</td>
<td>No data</td>
<td>Expensive</td>
<td>Production stability</td>
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<tr>
<td>GMO’s and Plants</td>
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<td>Cheap</td>
<td>GMO concerns</td>
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<td>Natural products</td>
<td>Some, but low activity</td>
<td>No data</td>
<td>V. Cheap</td>
<td>Lack of data</td>
<td>Soon?</td>
</tr>
</tbody>
</table>

Shatlock RJ IAS Rio de Janeiro 2005
Summary

• Effectiveness studies ongoing
  – PRO-2000 (MDP-310, HPTN-035)
  – BufferGel (HPTN-035)
• Phase 2B/3 results awaited in next 12 months
  – Carraguard
  – Mira diaphragm study (Replens Gel)
• VivaGel Phase 2 studies ongoing
• Polyanion microbicide “challenges” may impact broader microbicide field