Overview

- Rectal microbicide development
- Drug development pathway
- The CHARM Program
  - Overview
  - Progress to date
- Next steps in rectal microbicide development
Rectal Microbicide Development
Rationale

- Unprotected receptive anal intercourse (RAI) is the highest risk sexual activity for HIV transmission.
- Men and women in the developed and developing world practice RAI.
- Murine and non human primate studies have shown proof of concept that rectal application of ARV microbicides can prevent SIV/HIV infection.
## Phase 1 Rectal Safety Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Product</th>
<th>Status</th>
<th>Timeline</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>Tabet et al.</td>
<td>Nonoxynol-9</td>
<td>Completed</td>
<td></td>
<td>NIH</td>
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<tr>
<td>RMP-01</td>
<td>UC781</td>
<td>Completed</td>
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<td>NIAID/DAIDS</td>
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<td>RMP-02 / MTN-006</td>
<td>Tenofovir</td>
<td>Completed</td>
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<td>MTN-007</td>
<td>Tenofovir</td>
<td>Planned</td>
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<td>NIAID/DAIDS</td>
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<td>Project Gel</td>
<td>Tenofovir</td>
<td>Planned</td>
<td>Q1 2011</td>
<td>NICHD/R01</td>
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Drug Development
Drug Development

- Discovery
- Pre-clinical research
- IND application
- Clinical research
  - Phase 0
    - Pre-Phase 1
    - Phase 1
  - Phase 2
  - Phase 3
- Licensure
  - Phase 4
Integrated Preclinical / Clinical Program for HIV Topical Microbicides (IPCP-HTM)

Drug Discovery

Preclinical

Phase 1
RM Development and the IPCP Program

Pre-Phase 1  Phase 1  Phase 2  Phase 2B/3

IPCP  CHARM  IPCP  MDP

MTN (006, 007, 017)
The CHARM Program
Outline of CHARM Program

- **Project 1**
  - Nonclinical strategies for refining combination rectal formulations

- **Project 2**
  - Topical antiretrovirals to prevent rectal HIV infection

- **Project 3**
  - Exploratory human trials of combination rectal microbicides

- **Core A**
  - Administrative core

- **Core B**
  - Regulatory compliance and informatics core

- **Core C**
  - Formulation development core

Ian McGowan MD PhD, University of Pittsburgh
Formulation Development Core

Specific Aims:

- Manufacture a rectal specific microbicide product containing UC781
- Develop a rectal specific microbicide product containing TFV
- Develop a rectal specific combination microbicide containing TFV and UC781
- Development of biologically relevant product assessments for rectal microbicide products.
Background

- Most vaginal microbicides and sexual lubricants are not optimized for rectal use
## Formulation Characteristics

<table>
<thead>
<tr>
<th>Lubricant</th>
<th>Osmolality (mmol/kg)</th>
<th>pH</th>
<th>Viscosity (cps, 10 rpm @ 25°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen</td>
<td>321</td>
<td>8.1</td>
<td>4</td>
</tr>
<tr>
<td>PRÉ</td>
<td>502</td>
<td>7.3</td>
<td>1683</td>
</tr>
<tr>
<td>KY Jelly</td>
<td>2510</td>
<td>4.5</td>
<td>5913</td>
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<tr>
<td>ID Glide</td>
<td>3150</td>
<td>5.2</td>
<td>751</td>
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<tr>
<td>Elbow Grease</td>
<td>3865</td>
<td>5.7</td>
<td>3159</td>
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<td>Astroglide</td>
<td>6113</td>
<td>4.0</td>
<td>207</td>
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<tr>
<td>Gynol II (N9)</td>
<td>1245</td>
<td>4.7</td>
<td>1248</td>
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<tr>
<td>Wet Platinum</td>
<td>NA</td>
<td>NA</td>
<td>145</td>
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MDP Project 5 Aim 2

- Evaluation of placebo formulations
  - Aqueous gel and liquid
  - Lipid gel and liquid
- Endpoints
  - Safety and acceptability
  - Spreading
  - Intestinal permeability
  - Explant HIV infection

MDP Program: Peter Anton MD
## Current Tenofovir Formulations

<table>
<thead>
<tr>
<th>Units</th>
<th>Vaginal</th>
<th>Reduced Glycerin</th>
<th>Rectal Specific</th>
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</thead>
<tbody>
<tr>
<td>Tenofovir (%)</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Glycerin (%)</td>
<td>10</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>Viscosity (Cps)</td>
<td>9921</td>
<td>9423</td>
<td>3049</td>
</tr>
<tr>
<td>pH</td>
<td>4.5</td>
<td>4.6</td>
<td>7</td>
</tr>
<tr>
<td>Osmolality (Mmol/kg)</td>
<td>4055</td>
<td>1087</td>
<td>479</td>
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<td>Studies</td>
<td>RMP-02 MTN-006</td>
<td>MTN-007 Project Gel</td>
<td>CHARM</td>
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</table>
Core C Activities

- Develop rectal specific formulations (GLP)
- Define product stability
- Facilitate preclinical animal toxicology in collaboration with CONRAD
- Outsource production of GMP grade product for human studies
CHARM Program Projects
Project 1

- Nonclinical strategies for refining combination rectal formulations
- Specific Aims:
  - To compare the utility of biopsy tissue versus resected tissue for the evaluation of product safety
  - To evaluate rectal specific UC781, TFV and combination formulations for safety and efficacy
  - Effect of semen on product efficacy
  - Combination studies (Maraviroc, SPL7013, Griffithsin)

Charlene Dezzutti PhD, University of Pittsburgh
Intestinal Explant Tissue

Surgical samples

Endoscopic samples
Location of Colon Tissues

Surgery

Right side

0

0

Left side

Endoscopy

<table>
<thead>
<tr>
<th>Side</th>
<th>Surgery</th>
<th>Endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Left</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Intestinal Explant Models

- Polarized
  - Matrigel
  - Explant
  - Gelfoam
  - 0.6 mL medium

- Non-Polarized
  - Gelfoam
  - Explants
  - Medium
Testing Microbicides Using Explants

- Microbicide
- HIV
- HIV p24 ELISA

Immunohistochemistry for p24 at study endpoint – not feasible for colorectal tissue
Developing a qPCR method for detection of integrated provirus
Toxicity of Formulations

No apparent toxicity of any of the formulations on colorectal tissue. Epithelium is intact with the exception of the N9-treated explant.
Toxicity of Formulations (MTT)

No apparent toxicity of any of the formulations on colorectal tissue as determined by MTT assay. N=1; additional tissues will be done.
Efficacy of Tenofovir Formulations

TFV Therapeutic Index

<table>
<thead>
<tr>
<th></th>
<th>TFV Fluid</th>
<th>Fluid placebo</th>
<th>Gel</th>
<th>Gel placebo</th>
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</thead>
<tbody>
<tr>
<td>&gt;1200</td>
<td>&gt;2500</td>
<td>9.6</td>
<td>&gt;440</td>
<td>15.8</td>
</tr>
</tbody>
</table>
# Efficacy of UC781 Formulations

## UC781 API

- % Inhibition

## UC781 Formulations

- % Inhibition

## UC781 Therapeutic Index

<table>
<thead>
<tr>
<th></th>
<th>UC781 Lipid liquid (0.1%)</th>
<th>Lipid liquid placebo</th>
<th>UC781 lipid dilutions</th>
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<tbody>
<tr>
<td>UC781</td>
<td>&gt;8700</td>
<td>89.5</td>
<td>27</td>
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<tr>
<td>Lipid liquid</td>
<td>89.5</td>
<td>27</td>
<td>1531</td>
</tr>
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</table>
Project 2

- Topical antiretrovirals to prevent rectal HIV infection
- Specific Aims:
  - To determine the potential protective effect of UC781, TFV, or UC781/TFV to prevent rectal HIV infection

Victor Garcia PhD, University of North Carolina
Humanized Mouse Model
Humanized Mouse Model

- NOD/SCID mice
- Mice implanted with human fetal thymic and liver tissues
- Treated with sub-lethal dose of gamma radiation
- Transplanted with autologous human CD34+ cells
- NOD/SCID-hu BLT mice have T cells, B cells, and macrophages in GALT and can be infected with HIV

Protection of Humanized Mice From HIV*


*FTC/TDF Intraperitoneal
Project 3

- Exploratory human trials of combination rectal microbicides

- Specific Aims:
  - Assay optimization and cross validation
  - Rectal-formulated exploratory trials
    - UC781
    - TFV
    - UC781/TFV

Peter Anton MD, David Geffen School of Medicine at UCLA
Assay Optimization - Flow

Intracellular Interferon-γ release after ionomycin/PHA exposure
Pre-Phase 1 Study Design

- UC781, TFV, UC781/TFV
- Single dose rectal exposure (N=12)
  - Rectal specific formulation
  - Vaginal formulation
- General and mucosal safety
- Compartmental PK
- Explant challenge
- Distribution studies (SPECT/CT)
Update on CHARM Program
Life after UC781

- CONRAD have stopped further clinical development of UC781
- CHARM Program will need to be refocused
- Critical need to identify new API for combination product
- Ongoing discussions with the International Partnership for Microbicides (IPM)
Maraviroc (Selzentry®)

- CCR5 Antagonist
- Acts on human CCR5 receptor
- Licensed as antiretroviral for treatment of HIV infection
- Pfizer/ViiV Healthcare have licensed product to IPM
- Under development by IPM for HIV prevention:
  - Ring
  - Gel
  - Combination products
Tenofovir / Maraviroc Combination

- Attractive combination as product would act on virus (RT) inhibition and target cell (CCR5 antagonism)
- Extensive preclinical testing
- GMP and prototype products already available
Next Steps in Rectal Microbicide Development
MTN-007

N=60

2% N-9 (N=15)

1% Tenofovir (N=15)

Baseline Evaluation

Single dose

7-14 day interval

7-14 day interval

7 day daily doses

HEC (N=15)

No Treatment (N=15)

Endoscopy Safety/behavioral assessment

Screening
**Project Gel**

**Stage 1A**
- Screening
- 240 MSM
- Consensual RAI in last month
- URAI in last year

**Stage 1B**
- 3 month Acceptability & Adherence study with placebo gel
- 120 MSM
- RAI in last 3 months
- STI negative

**Stage 2**
- Phase 1 tenofovir rectal safety study
- 42 MSM
- 80% adherence in Stage 1B

McGowan & Carballo-Diequez 2009
Populations for RM studies

- Phase 2 studies
  - RAI sexually active men and women
  - Higher risk populations
- Phase 2B studies
  - 3% seroincidence MSM populations
    - North America
    - Latin America
    - Asia
    - Africa
MTN-017

- Phase 2 expanded safety study of TFV (reduced glycerin formulation), Truvada (oral), and TFV/Truvada combination
- International study
  - United States
  - Thailand
  - Peru
- Safety, PK/PD, acceptability
- Foundation for Phase 2B study
- MTN concept approved and study moving towards protocol development
The CHARM program will focus on the development and evaluation of rectal specific microbicides.

Initial studies (preclinical and clinical will involve tenofovir)

Ongoing discussions to secure 2\textsuperscript{nd} product – lead candidate Maraviroc

Other Phase 1/2 studies ongoing or in planning stage
Funding Acknowledgements for Ongoing RM Research

- NIH/NIAID/ DAIDS
  - U19 AI060614
  - U19 AI082637
  - U01AI068633-01

- NIH/NIAID/DMID
  - U01 AI066734

- NIH/NICHD & NIH/NIMH
  - R01 HD059533-01A1
Questions?