PREVENT
Griffithsin-based Rectal Microbicide Development Program

Kenneth E. Palmer, Ph.D.
Griffithsin (GRFT)

- **Griffithsia**, red alga originally collected off Chatham Island New Zealand
  - Used for nutritive and traditional medicine
- Aqueous extract displayed potent anti-HIV activity
- Active constituent appeared to be a protein, one of the most potent HIV-1 entry inhibitors
- Active component is a lectin that targets the dense clusters of sugars (glycans) present on the surface of HIV
HIV-1 Envelope Glycosylation

HIV-1 Oligomannose Glycans

Man-9

CD4 binding site

Figure courtesy of Chris Scanlan (University of Oxford)
Manufacturing of GRFT
Griffithsin Activity Against HIV-1

- **In vitro**, Griffithsin has mid picomolar to low nanomolar entry inhibitor activity against a broad range of primary HIV-1 isolates from all clades tested to this point.
- GRFT shows good synergy *in vitro* with ARV from other classes e.g. TFV, RAL, MVC

- Persistent HIV inhibitory activity in pre-treated PBMC suggests that surface-bound GRFT retains antiviral activity.
- GRFT prevents infection of polarized colorectal tissue to 1 µM. C. Dezzutti, unpublished.
Griffithsin Carbopol Gel Protects Mice from Genital Herpes (HSV-2) Infection

- **Note enhanced efficacy in presence of SP**

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Griffithsin Protects Mice from Genital Herpes by Preventing Cell-to-Cell Spread

Multipurpose Prevention Applications for GRFT-Based Microbicides

- GRFT has potent activity *in vitro* against HIV-1; HIV-2; hepatitis C virus
- HCV inhibitory activity suggests applications for prevention in HIV positive MSM at risk for HCV and HIV-1 superinfection
PREVENT PROGRAM STRUCTURE
GRFT PREVENT RECTAL GEL

• Rectal Gel
• First generation product:
  – Single active ingredient GRFT
  – Prevention of HIV transmission
    • Prevention of HCV and HSV-2 transmission
• Second generation product: co-formulation with ARV
• First in man clinical trial will enroll 18 healthy MSM volunteers to test first generation gel product
  – Single dose administration for safety assessment
  – Multiple dose safety assessment
PREVENT PROGRAM TIMELINE

2015
Pre-IND Meeting with FDA
Develop Optimal Gel Formulation
Test Formulation in Monkeys
Perform Preclinical Safety Studies
File IND with FDA
Perform First-in-Man Clinical Trial
Analyze Results

2016

2017

2018

2019
ACKNOWLEDGEMENTS

• PREVENT Team
  – Daniel Tusé, Ph.D. Intrucept Biomedicine
  – David Garber, Ph.D. CDC, Atlanta
  – Ross Cranston, M.D. University of Pittsburgh
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  – Ian McGowan, M.D., Ph.D. University of Pittsburgh

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Development of a Rectal Enema (Douche) as Microbicide (D.R.E.A.M.): PrEP that People will Enjoy Using

Craig W. Hendrix, MD
Johns Hopkins University
DREAM Program Objective

Develop a TFV prodrug enema/douche to provide HIV protection for one week after receptive anal intercourse

Exploit behaviorally-congruent PrEP formulation to mitigate adherence concerns
Adherence Biggest Cause of PrEP Failure

Vrijens & Urquhart CPT 2014

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral FTC/TDF for women (FEM-PrEP, Kenya, South Africa, Tanzania)</td>
<td>6% (-52, 41)</td>
</tr>
<tr>
<td>1% Tenofovir vaginal gel (CAPRISA 004, South Africa)</td>
<td>39% (6, 60)</td>
</tr>
<tr>
<td>Oral FTC/TDF MSM (IPrEX, Americas, Thailand, South Africa)</td>
<td>44% (15, 63)</td>
</tr>
<tr>
<td>Oral FTC/TDF for young heterosexuals (TDF2, Botswana)</td>
<td>62% (22, 83)</td>
</tr>
<tr>
<td>Oral TDF and oral FTC/TDF for HIV serodiscordant couples (Partners PrEP, Kenya, Uganda)</td>
<td>67% (44, 81)</td>
</tr>
<tr>
<td>Partners PrEP (Adherence substudy, n = 1,147)</td>
<td>100% (84, 100)</td>
</tr>
</tbody>
</table>

% Efficacy
% Adherence

DREAM
DEVELOPMENT OF A RECTAL ENEMA AS MICROBICIDE
Douching is commonly part of anal sex

Positive Medicated Douche Marketing

Fleet Naturals is a hygienic approach to personal cleansing ready to use right from the box. Each non-medicated enema is fragrance-free, with all-natural aloe and a flexible Comfortip® pre-coated with a water-based lubricant. For an easy way to clean from a brand you can trust, look no further than the digestive care also for clinically tested, doctor-recommended Fleet Naturals.

Learn More
Positive Medicated Douche Marketing

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Learn More

& safe
What formulation do we need?

- People use a variety of applicators
  - Bottles, bulbs, “sinkers,” bidets, shower attachments, etc.
  - Are these all suitable for delivery of a medicated douche?
- What applicator/bottle will we use?
- Will the product be portable?

We should develop a product accepted by users
Will a Douche “Cover” HIV in the colon?

“Microbicide”\(^{(111}\text{In-DTPA)}\) vs “HIV” \(^{(99}\text{mTc-SC)}\) in Ejaculate

Rectal TFV gel (0h), simulated sex/ejaculation (1h), SPECT/CT (2h)
Does the drug contact the mucosa?

Hypotonic Saline (NaCl)
Excellent drug-mucosal contact

Hypertonic Saline (~Fleet)
Poor drug-mucosal contact

Maisel K. J Control Rel 2015
What Concentration is Protective?

- iPrEx EC$_{90}$ 16 fmol/10$^6$ cells (3-28 95% CI) (Anderson STM 2012)
- Colored panels, adherence benchmarks (STRAND DOT IQRs)
- Other studies relate protective PBMC TFV-DP to estimate colon tissue TFV-DP tissue concentrations (Anton ARHR 2012, Hendrix CROI 2012, Louissaint ARHR 2013)
How soon is HIV protection achieved?

C30min

- Rectal Tissue Cell TFV-DP (fmol/M cells)
- Single Oral
- Single Rectal
- Multiple Rectal

One week with daily oral dosing
Half-hour with rectal dosing

C24h

- Rectal Tissue Cell TFV-DP (fmol/M cells)
- Single Oral
- Single Rectal

One day later, it’s still going up

RMP-02/MTN-006 Yang, et al. PLOS One 2014
Planned Product Enhancement

TFV enema PK Enhancements
- Absorption
  - TFV analogs
  - Hypotonic vehicle
- Sustained release
  - Nanoparticle
  - Gelling agent

Reference Targets
- Colon CD4+ cell TFV-DP
- Bridging RCT-PK studies

Contributions: Yanhui Lu

Contributions:

Hours

Tenofovir diphosphate fmol/10^6 colon CD4+ cells

Naked TFV

0 24 48 72 96 120 144 168

0 100 200 300 400 500

4/wk

2/wk

Target

0 200 400 600

0 100 200 300 400

Tenofovir diphosphate fmol/10^6 colon CD4+ cells

Naked TFV
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**Graph:**
- Absorption-enhanced TFV
- Sustained release & Absorption-enhanced TFV
- Naked TFV
- Sustained release-enhanced TFV

**Axes:**
- Tenofovir diphosphate fmol/10^6 colon CD4+ cells
- Hours

**Legend:**
- 4/wk
- 2/wk
- Target

**References:**
- Colon CD4+ cell TFV-DP
- Bridging RCT-PK studies
DREAM Program Studies

• Clinical
  – DREAM 01: TFV dose escalation, hypotonic saline
  – DREAM 02: Sex-enema/enema-sex distribution effect
  – DREAM 03: Compare optimized TFV vs. TFV prodrug

• Pre-Clinical (mice, macaques)
  – Select optimal saline for clinical studies
  – Select optimal TFV prodrug for TFV comparison
  – Compare TFV v. TFV analog nano/thermoreversible gel
DREAM 01 Study Design Overview

• Open label, sequential 3 product, single dose
• 18 healthy volunteers across 3 sites (JHU, UCLA, Pitt)

• Products
  – 1x (≈TFV 1%), 3x (<5 day TFV 1%), 6x (hypotonic 3x)
  – 125 mL + NaCl (normal saline or half-normal saline)
  – 1 dose in clinic, 3 doses at home with RAI

• Assessments
  – Safety: clinical, histology, transcriptomics/proteomics
  – Acceptability: questionnaire, interview
  – Drug concentration in blood and rectal tissue
  – Drug activity: ex vivo HIV explant challenge
Thank you!
Can rectal TFV protect as well as oral?

<table>
<thead>
<tr>
<th>Matrix</th>
<th>14C-TDF*</th>
<th>RMP-02/MTN-006</th>
<th>Rectal vs. Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Matrix</td>
<td>Single oral</td>
<td>Single Rectal</td>
</tr>
<tr>
<td>Plasma TFV ng/mL (LLOQ 0.31)</td>
<td></td>
<td>40 (24, 51)</td>
<td>35.8 (21.4 - 54.9)</td>
</tr>
<tr>
<td>Tissue homog. TFV ng/mg (LLOQ 0.14)</td>
<td></td>
<td>0.03 (BLQ, 0.21)</td>
<td>BLQ (BLQ-14.6)</td>
</tr>
<tr>
<td>Tissue homog. TFV-DP fmol/mg (LLOQ 17)</td>
<td></td>
<td>7.5 (3.5, 60.9)</td>
<td>BLQ (BLQ - 991)</td>
</tr>
<tr>
<td>Colon Total Cell TFV-DP fmol/M cells (LLOQ 160)</td>
<td></td>
<td>25 (15, 88)</td>
<td>BLQ (BLQ - 227)</td>
</tr>
<tr>
<td>Colon CD4+ TFV-DP fmol/M cells (LLOQ 229)</td>
<td></td>
<td>1 (BLQ, 4)</td>
<td>BLQ (BLQ – BLQ)</td>
</tr>
</tbody>
</table>

* LLOQ do not apply to 14C-TDF study which used AMS
** Ratio of median C_{24} Day 5 rectal gel to median C_{24} Day 1 rectal gel

5 rectal doses may not yet have achieved at steady-state based on PBMC TFV-DP concentrations.

- **Rectal dose achieves 266 x greater colon CD4+ TFV-DP than oral**
- **5 daily rectal gel doses achieves 4x single dose colon CD4+ TFV-DP**
- **Rectal dose only 1% of oral dose systemic exposure**
Would you like an Enema or Douche?

**Enema**
- Constipation
- Preparation for medical procedures
- Illness

**Douche**
- Cleansing
- Eliminating odor
- Getting ready for sex
Are Douches safe?

- Rectal douching associated with increased risk for HIV transmission (Coates 1988, Moss 1988)

- Tap water & hyper-osmolar enemas show colonic epithelium damage (Meisel 1977, Schmelzer 2004)

- Rectal hyper-osmolar gels induce greater epithelial loss than iso-osmolar gels (Fuchs 2007)
MTN-026/IPM 038

Ross D. Cranston MD FRCP
Associate Professor
University of Pittsburgh
A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults
Products

- Dapivirine 0.05%
- HEC Placebo Gel
Dapivirine

- NNRTI
- Increased potency compared to tenofovir in *in vitro* testing
- Safe and acceptable in MTN-012 (penile tolerance study)
- API in the ASPIRE Ring study
Study Summary

- Phase 1, multi-site, randomized (2:1), double-blind, placebo-controlled trial
- 24 evaluable HIV-uninfected men and women aged 18-45 years inclusive
- Approximately 42 days of follow-up per participant is planned with a projected accrual period of 6-8 months
- Participants will be randomized to receive either a single dose of dapivirine gel or universal HEC placebo gel rectally, followed by 7 daily doses of the same product to be administered under direct observation in the clinic
Study Visit Schedule

V1: Screening >30 Days

V2: Enrollment Visit ~7 Days

V3: Rectal Application Directly Observed Dose

V4: 24 hr

Intensive Sampling at Either 24 hrs or 48 hrs

V5: 48 hr

V6: 72 hr

V14: 24 hr

V15: 48 hr

V16: 72 hr

V7-V13: 7 Rectal Applications - Directly Observed Dosing

V17: Follow-up Contact ~7 Days

V14: 24 hr

V15: 48 hr

V16: 72 hr

Intensive Sampling at Either 24 hrs or 48 hrs
Primary Objectives/Endpoints

- **Safety**: To evaluate the safety of dapivirine gel formulation when applied rectally
  - Grade 2 or higher AEs
- **Pharmacokinetics**: To characterize the systemic and compartmental pharmacokinetics of dapivirine gel following rectal application
  - Dapivirine concentrations
    - Blood,
    - Rectal fluid
    - Rectal mucosal tissue homogenates
Secondary Objectives/Endpoints

- **Acceptability**: To identify product attributes considered likely to challenge and facilitate future sustained use of rectally applied dapivirine gel
  - Product attributes considered likely to challenge future sustained use.

- **Mucosal Safety**: To evaluate the mucosal safety of dapivirine gel when applied rectally
  - Mucosal Safety (rectal proteomics/transcriptome/microflora/histology) and rectal tissue flow cytometry
Timeline

- Protocol development meeting  Dec 2014
- PSRC  Feb 2015
- PSRC approval  Mar 2015
- Projected Version 1.0  May 2015
- Projected start date  Oct 2015
Acknowledgements

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- IPM
Thank You