Overview of Non RT-Microbicides

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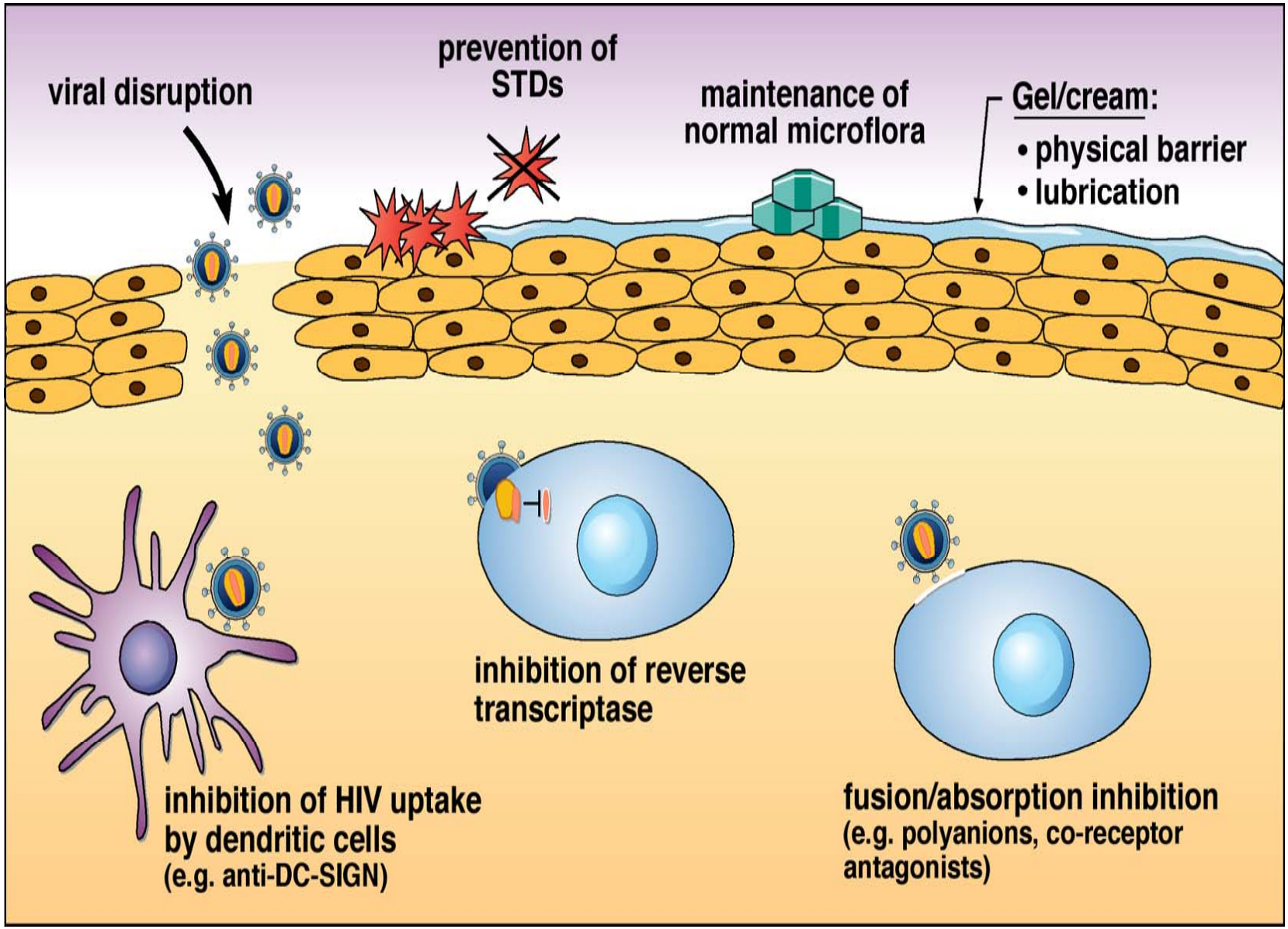
Overview

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



McGowan Biologicals 2006

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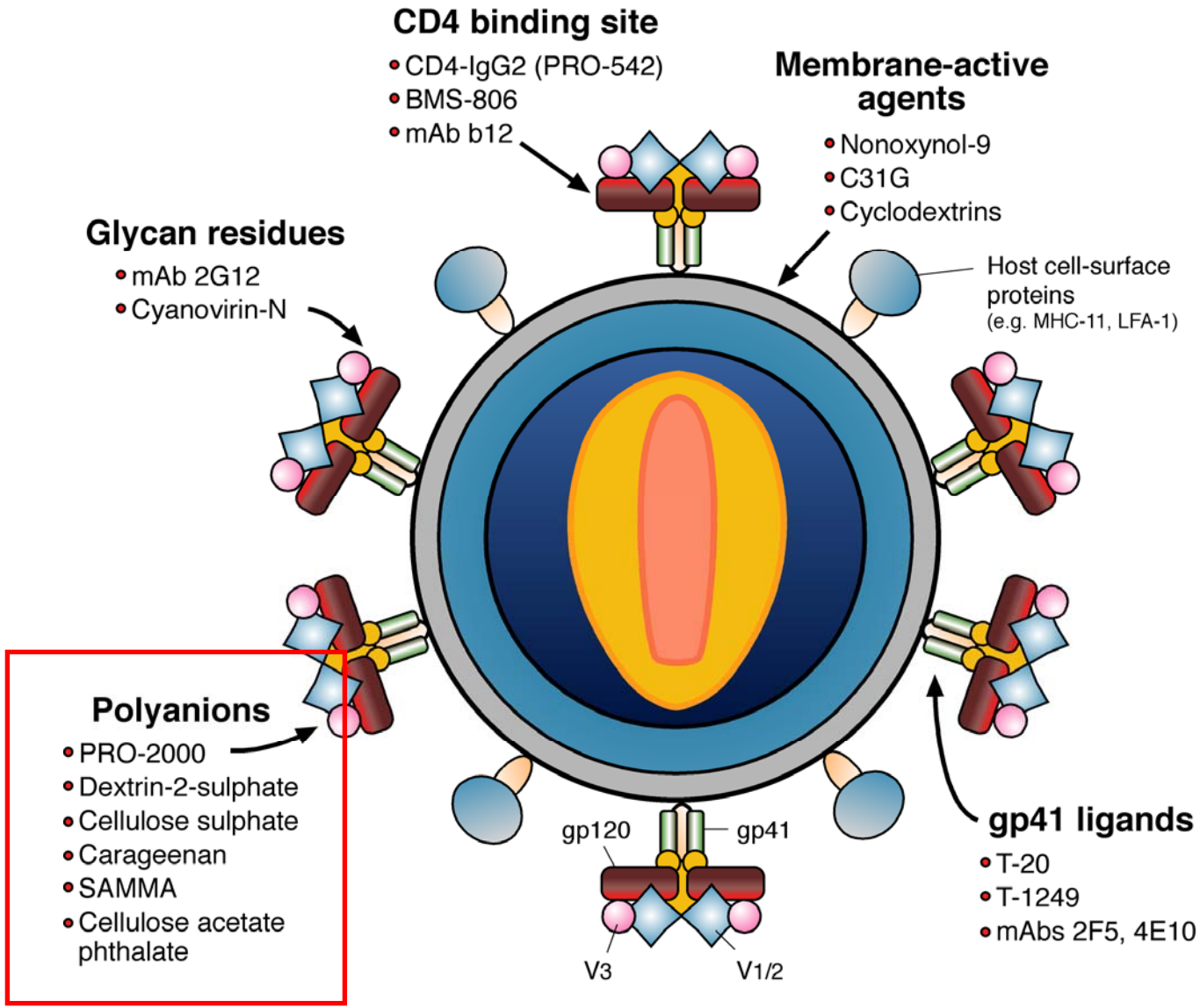

Adapted from Shattock and Moore, Nat Rev Microbiol, 2003

Microbicide Pipeline

	Pre-Clinical	Safety	Efficacy
Entry Inhibitors	Cyanovirin BMS806 Plant lectin	SPL7013 CAP Polystyrene sulfate	Pro2000 Carraguard Buffergel
NRTI & NNRTI	DABO	PMPA UC-781 TMC-120 MIV-150	
Membrane active		SLS	
Unclassified	Bacteria	Praneem	
Combination	PC-815 Truvada NRTI/NNRTI NRTI/P NNRTI/P		

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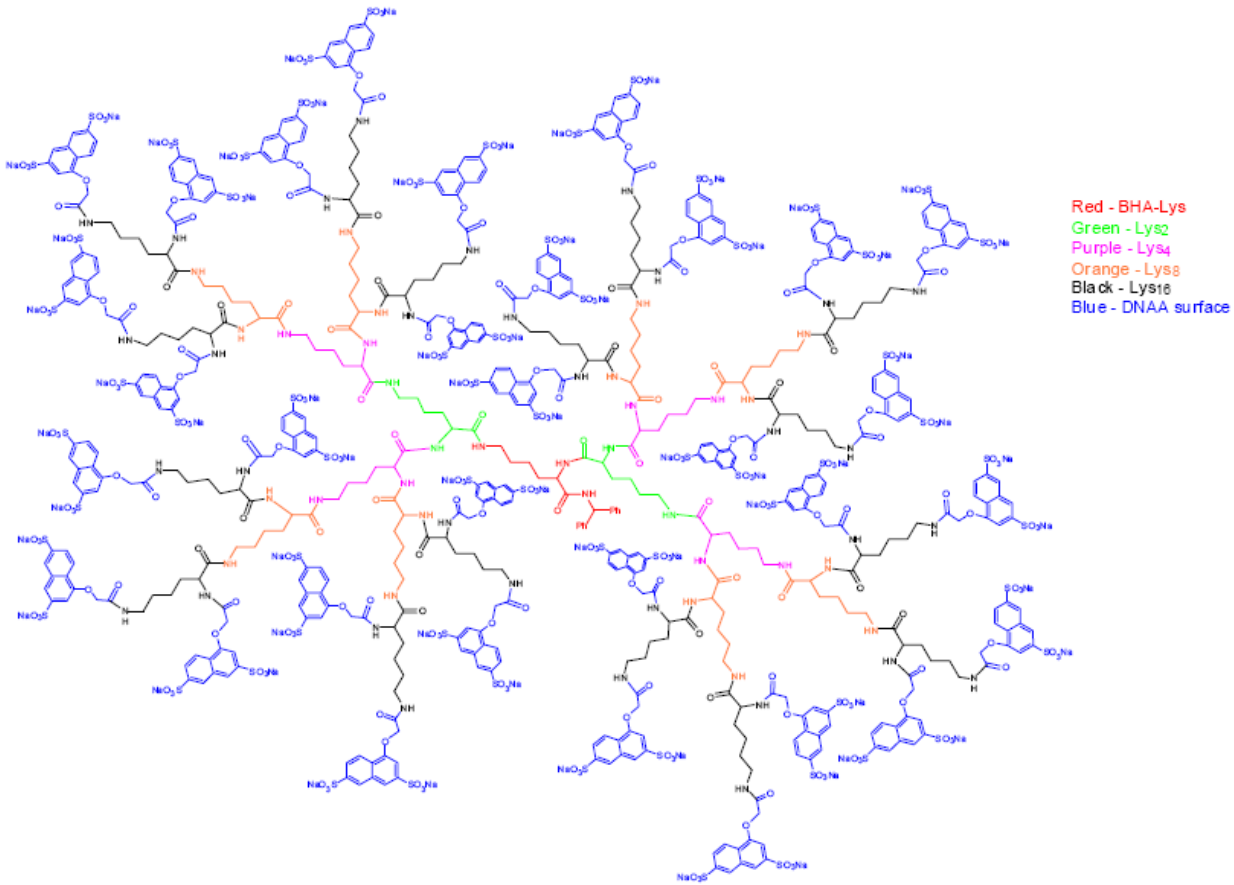
SPL7013

(VivaGel™)

SPL7013 (VivaGel™)



SPL7013 (VivaGel™)

- Polylysine dendrimer molecule with 32 copies of naphthalene-3, 6-disulfonate
- In vitro activity 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

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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

Arm	Description	N	Frequency
1	SPL7013 Gel	20	BID (14 days)
2	Placebo Gel	20	BID (14 days)

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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

Activity	Screen 1	Screen 2	Enroll	Phone Call (D2)	Week 1	Week 2	Week 3
Consent							
Screening	X	(X)					
Safety bloods	X	(X)	X		X	X	
Pelvic exam			X		X	X	X
Colposcopy			X			X	
PK			X			X	
Behavioral			X			X	
Vag culture			X		X	X	X
Innate factors			X		X	X	X

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

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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

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MTN-004 Timelines

Activity	Due Date	Status
Protocol development	November 2006	Completed
PSRC Review	December 2006	Completed
Response to PSRC	December 2006	Completed
Protocol sign off by DAIDS MO	December 2006	Completed
IRB Submission	January 2007	Completed
Protocol Registration	May 2007	Pending
Screening and enrollment	June 2007	Pending
Study completion	December 2007	Pending

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

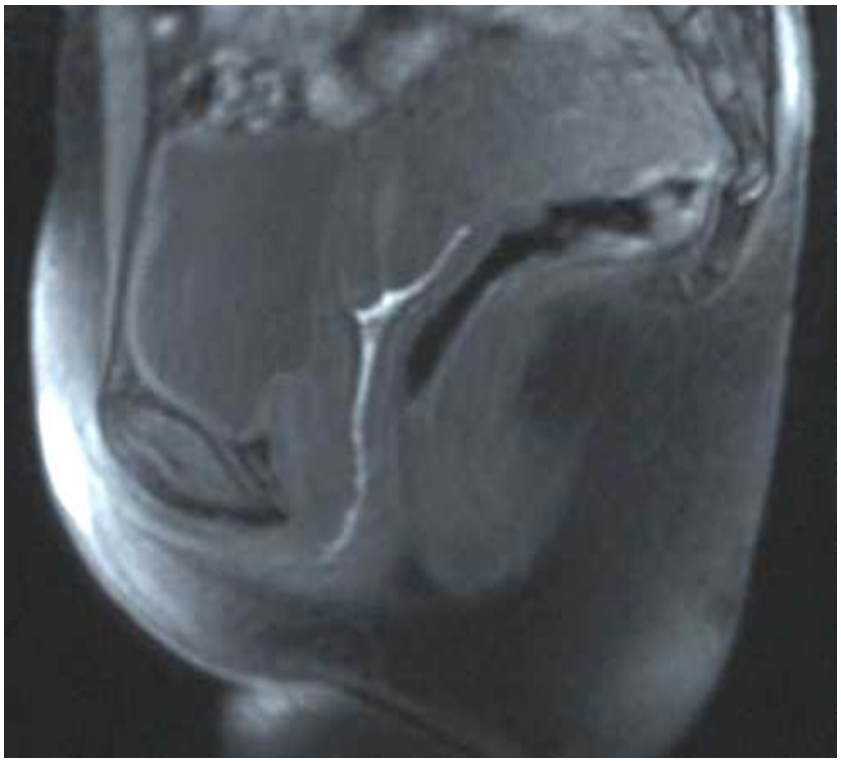
- Identified as a candidate microbicide through an excipient-screening program designed to identify compounds with anti-HIV-1 activity
- An anionic polymer belonging to the polycarboxylate group
- CAP works through blocking gp120 binding and induction of ‘‘dead-end’’ gp41 six-helix bundle formation
-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

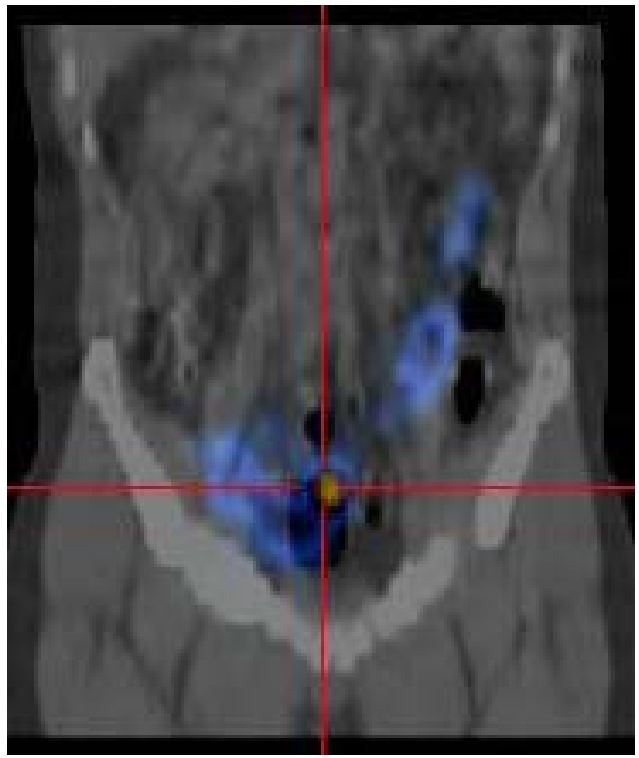
Formulation Innovations

New Formulations

- First generation of formulations were not optimized for vaginal or rectal use
- 2nd 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

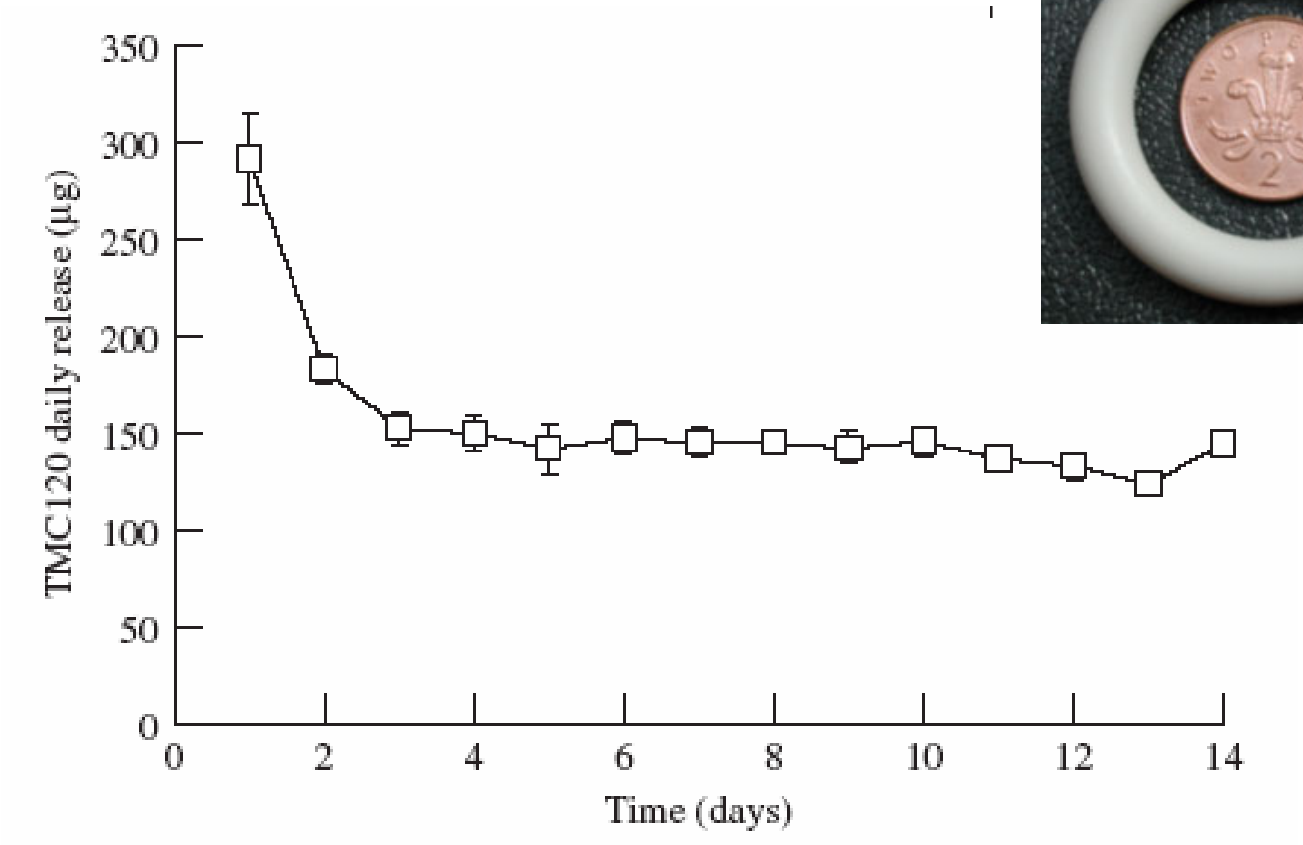
Imaging Where the Product Goes





Charles Lacey MD, & Craig Hendrix MD

TMC120 Vaginal Rings



Malcolm et al., Journal of Antimicrobial Chemotherapy, 2005

Rectal Microbicides

Prevalence of Anal Receptive Sex

Population	N	Prevalence of AI	Reference
MSM in EXPLORE study	4295	48 – 54%	Koblin et al. 2003
High risk women	1268	32%	Gross M et al. 2000
College students	210	20%	Civic D 2000
US Survey 15 – 44 years NSFG	12,571	35-40%	Mosher WD et al. 2005
Californian residents	3545	6-8%	Erickson PI et al. 1995

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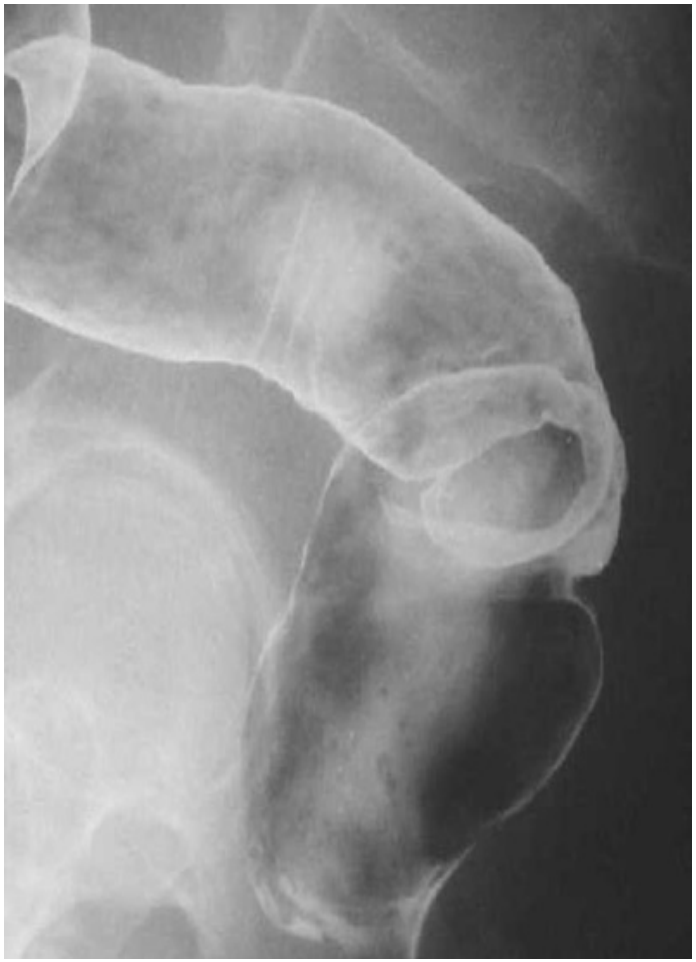
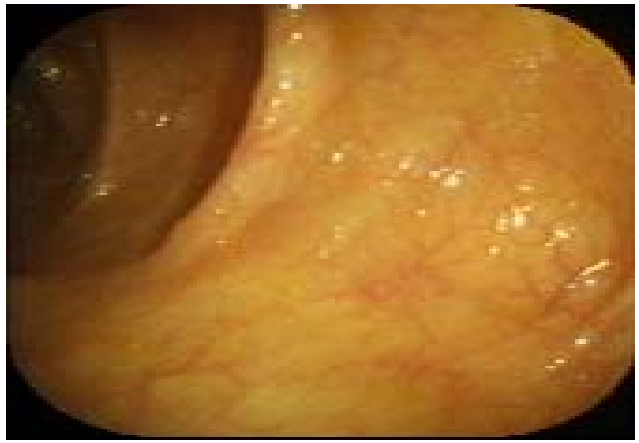
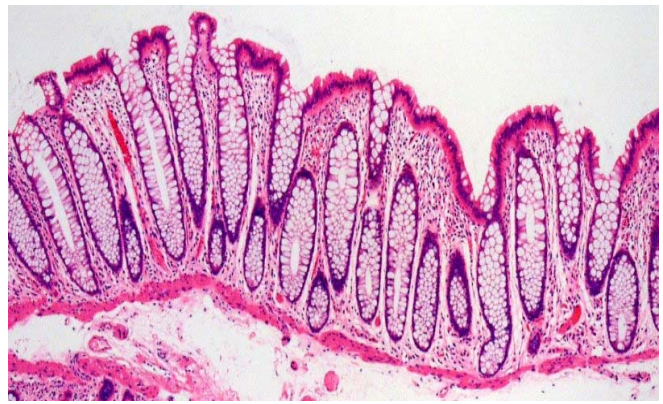
Women and RAI Outside the US

Country	Ever Experienced RAI (%)	Source
Brazil	31.0	Guimares MD et al. 1995
Peru	12.0	Caceres C et al. 1997
South Africa	42.8	Karim SS and Ramjee G 1998
Kenya	40.8	Schwandt M et al. 2006

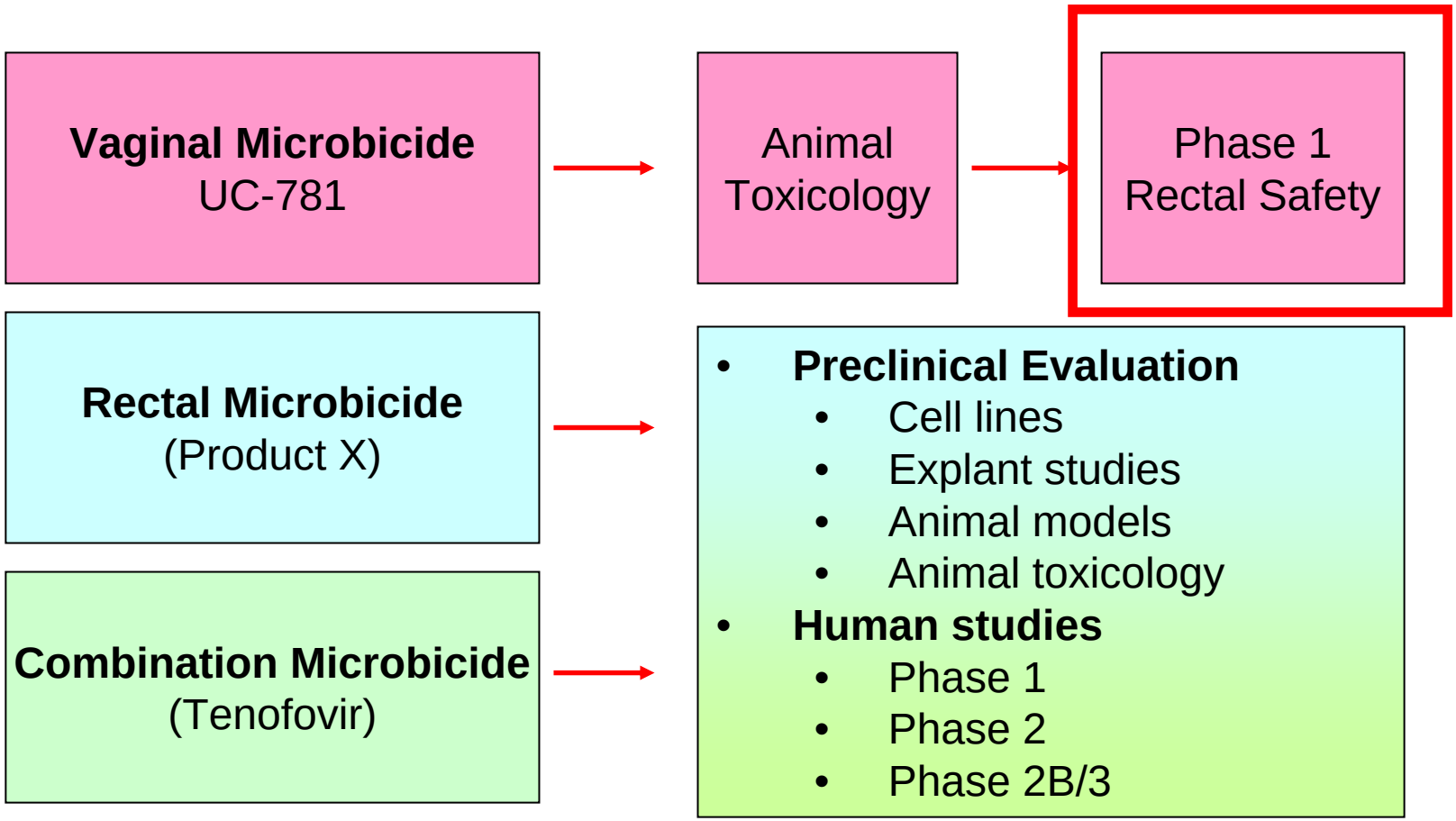
Rectosigmoid Anatomy







Rectal Safety Assessment



Design of UC-781 Phase 1 Rectal Safety Study

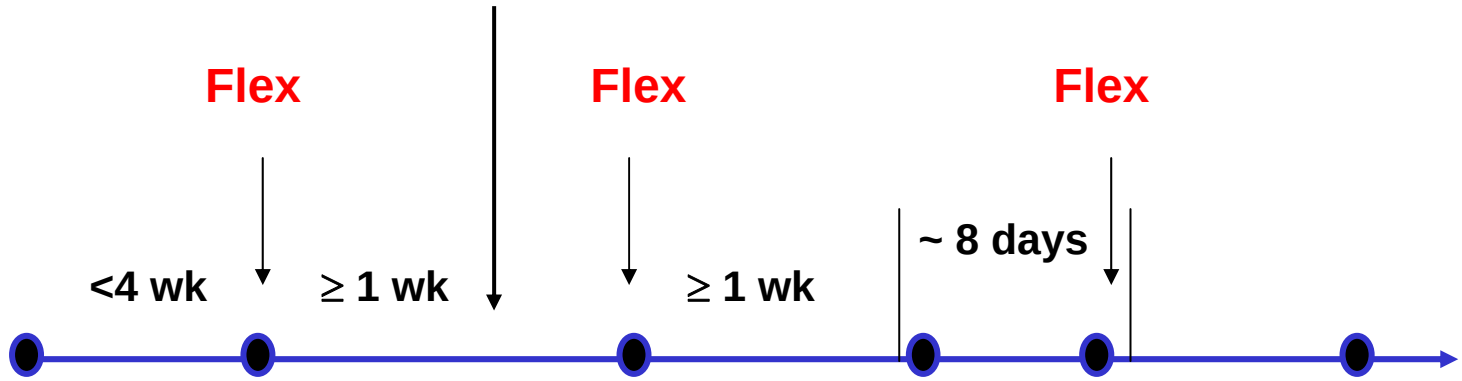
- Three arms (Men and women with history of RAI)
  - 0.1% UC-781 (N = 12)
  - 0.25% UC-781(N = 12)
  - Placebo (N = 12)
- Single dose followed by 7 days of study drug

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

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

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Applicator Design

Courtesy of Dr. Alex Carballo-Dieguez/amfAR

The Rectal Phase 1 Pipeline

Phase 1RM Safety Studies

Product	Status	Timeline	Sponsor
UC-781	Ongoing		NIAID/DAIDS
TBN	Planned	Q3 2007	NIAID/DMID
PRO-2000	Planned	Q1 2008	MDP MRC-UK
UC-781 (Rectal formulation)	Possible	Q4 2010	TBD

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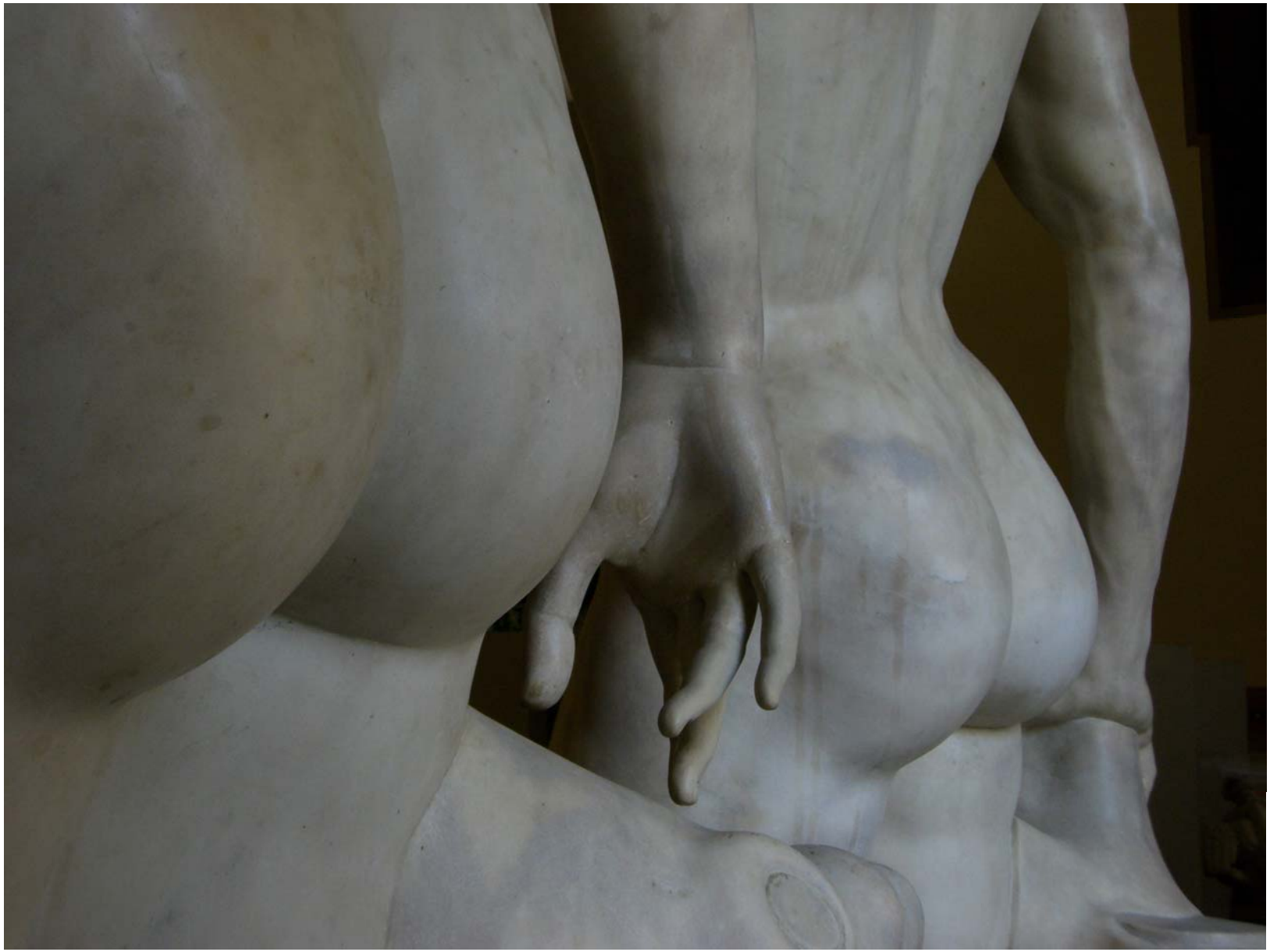


Bargello Museum, Florence, Italy

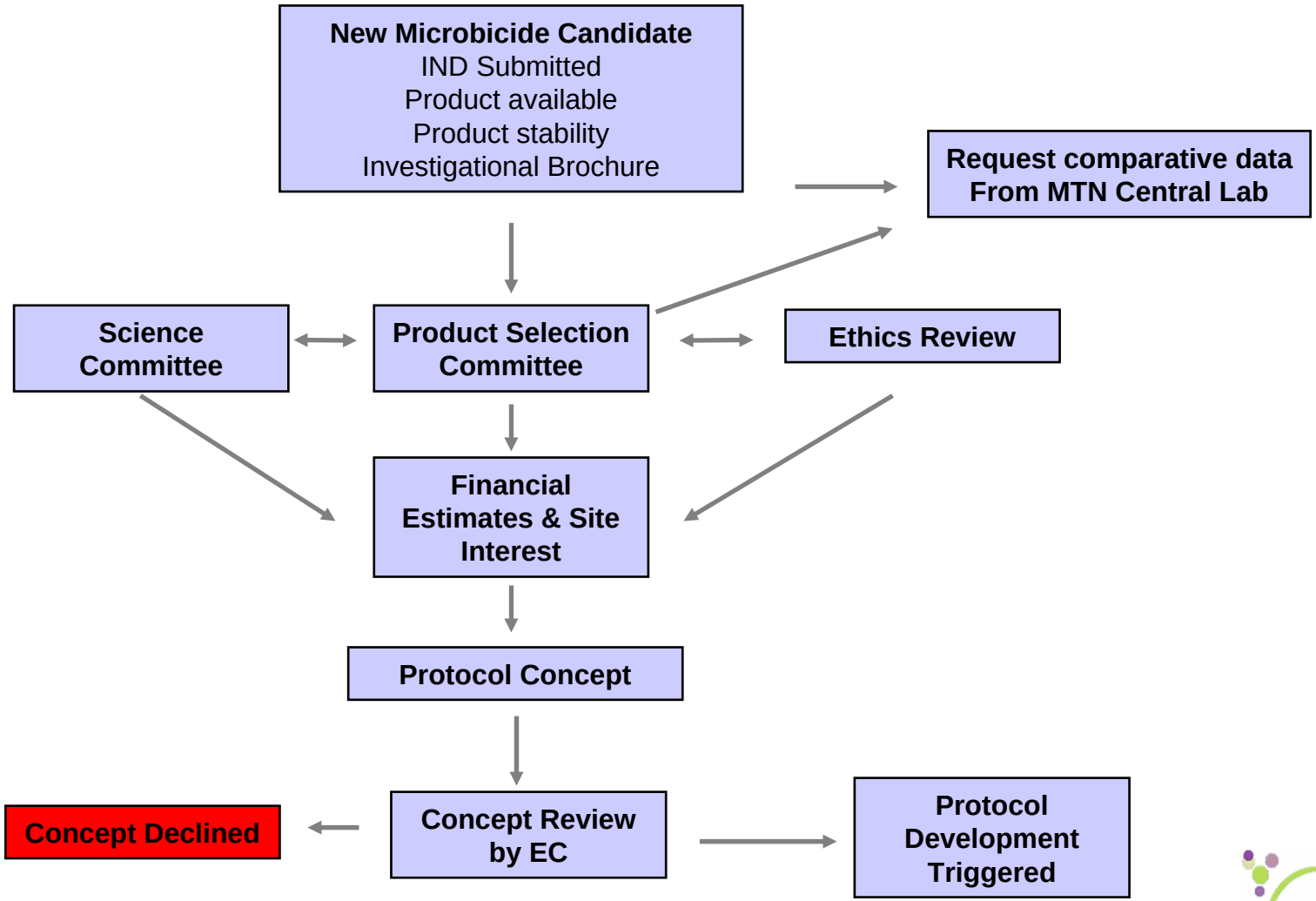
The MTN Pipeline

Requirements for MTN Assessment

New Microbicide Candidate

- IND Submitted
- Product available
- Product stability
- Investigational Brochure

Concept Development and Approval Process



What Products Might be Realistically Useful to MTN?

MOA	Preclinical	Phase 1	Phase 2	Phase 2B
Fusion / Entry Inhibitors	GSK-769	CAP	VivaGel™	
RTI		GSK-248	UC-781 TMC-120	Tenofovir
Integrase		GSK-364735		
CCR5	RANTES analogues	SCH-C, D UK-427,857		

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Summary

The Microbicide Pipeline in 2007

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

Shattock RJ IAS Rio de Janeiro 2005

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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

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