

The MTN Pipeline

Ian McGowan MD PhD FRCP

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Overview

- Microbicide development
- The microbicide pipeline?
 - Generic
 - IPM
 - CONRAD
 - Other
- The current MTN portfolio
- Future opportunities for the MTN

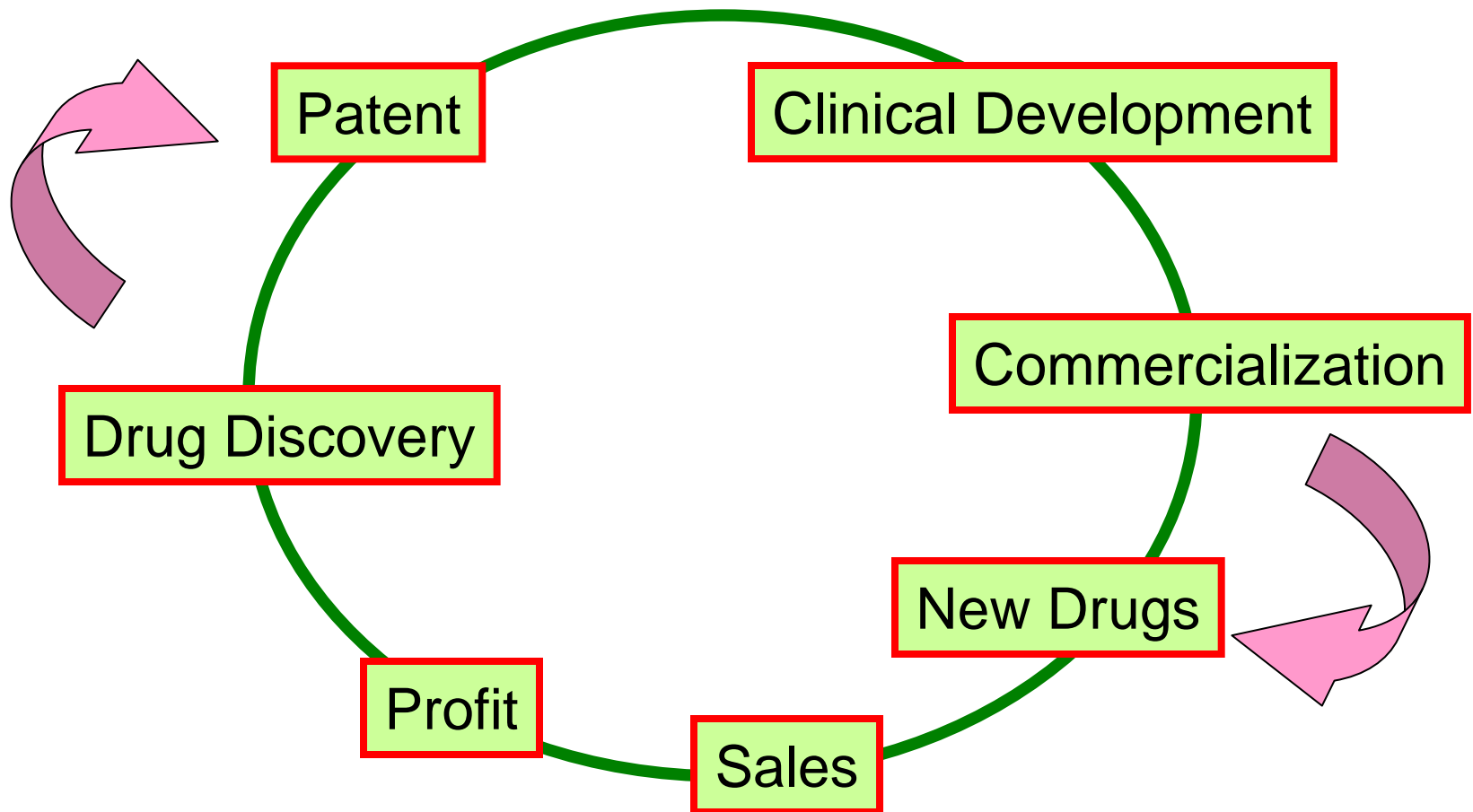
Microbicide Development

Drug Development

- Discovery
- Pre-clinical research
- IND application
- Clinical research
 - Phase 1
 - Phase 2
 - Phase 3
- Licensure
 - Phase 4



What Motivates Drug Development?





MTN Requirements

- IND Submitted
- Initial preclinical toxicology completed
- Product stability data available
- Investigator brochure
- GMP CTM available

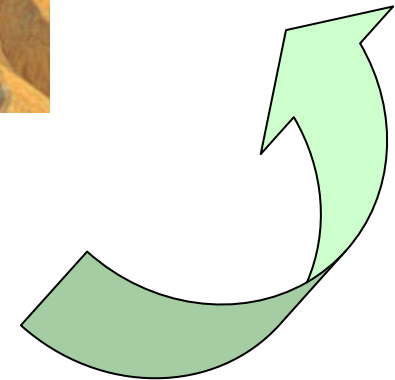
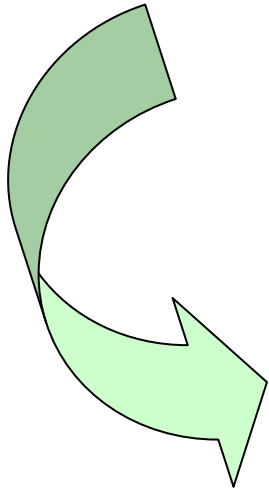
First Challenge: The Valley of Death



Drug
Discovery

Phase 1

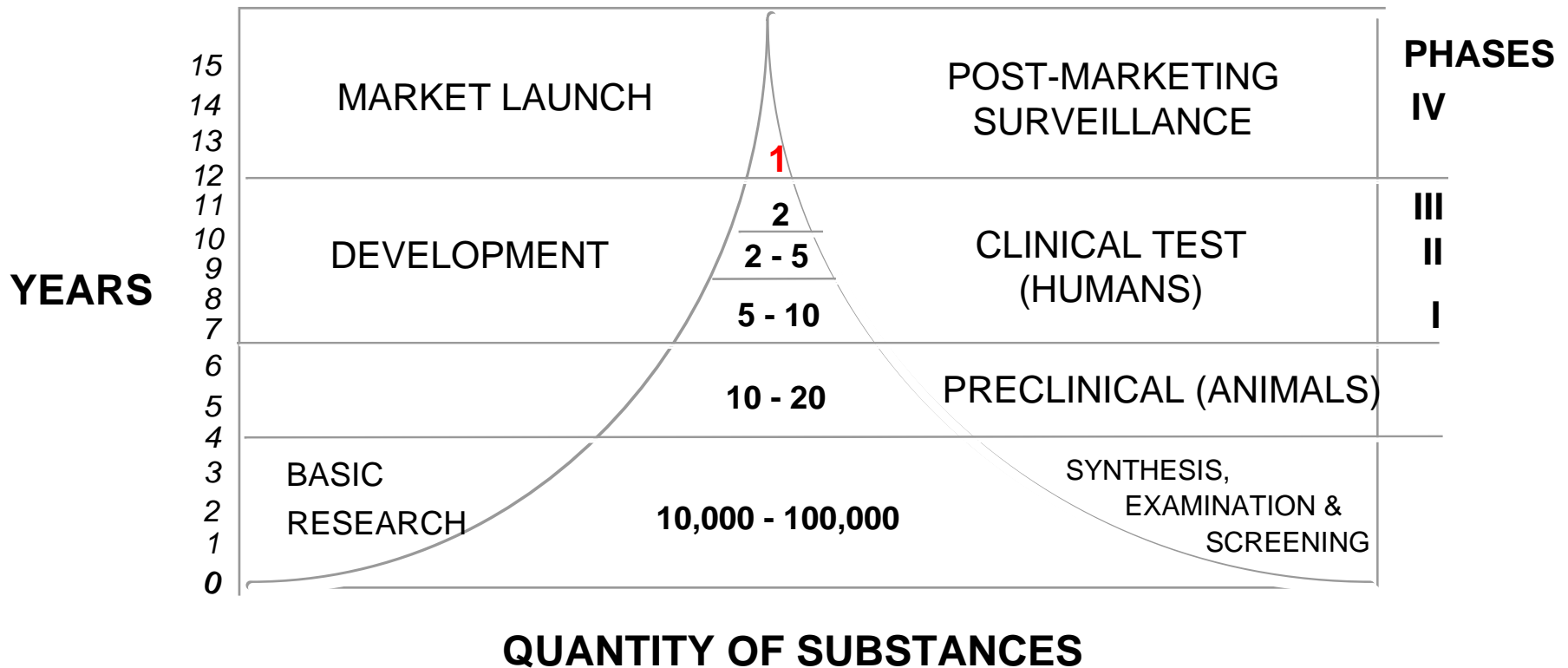
Preclinical



FDA Preclinical Requirements

- Secondary & Safety Pharmacology
 - Vaginal microbial activity testing
 - Receptor screens
 - Enzyme assays
 - CNS & PNS (Rat Irwin)
 - Respiratory system
 - Cardiovascular system
 - Dog telemetry
 - Purkinje Fiber
 - HERG assay
- Pharmacokinetics
 - Absorption
 - Distribution
 - Metabolism
 - Excretion
 - Drug interactions
- General Toxicology
 - Acute - mice and rats (oral & IV)
 - Sub-chronic (4 weeks)
 - Rats and rabbits (intravaginal)
 - Other routes?
 - Chronic
 - rat (6 months) & rabbit (9 months)
- Reproductive Toxicology
 - Fertility & reproductive performance (rat)
 - Embryofetal development (rat & rabbit)
 - Peri- & post-natal development (rat)
- Genotoxicology
 - In vitro – microbial & mammalian cell
 - In vivo – micronucleus test (mouse or rat)
- Carcinogenicity
 - 2 years (mouse & rat)
- Other
 - Sensitization assay
 - Sperm toxicity
 - Vaginal biomarkers (pro-inflammatory/innate immunity)

Drug Development is High-Risk



Source: Based on PhRMA analysis, updated for data per Tufts Center for the Study of Drug Development (CSDD) database.

On average, it takes ~15 years & >800 million dollars to make a drug

What is the Microbicide Pipeline?

Generic Pipeline

Microbicide Candidates

Uncertain	Defense Enhancers	Entry / Fusion Inhibitors	
<ul style="list-style-type: none"> □Ciclopiroxolamine □Praneem polyherbal 	<ul style="list-style-type: none"> □MucoCept HIV □Acidform™ gel □BufferGel™ 	<ul style="list-style-type: none"> □Cellulose sulfate □Cellulose acetate □Carraguard □VivaGel □Dextrin-2 sulfate □Cyanovirin-N □C85FL □K5-N, OS(H) □SAMMA □Invisible condom □Novaflox □Porphyrins □PSC Rantes □BMS-806 □BMS-378806 □CMPD167 	<ul style="list-style-type: none"> □C52L □Tobacco-derived antibodies / fusion proteins □Anti-ICAM-1 Ab mAb B12, 2G12 □mAb 2F5, 4E10 □CD4 IgG2 □T20 □T-1249 □SCH-C, D □UK-427,857 □TAK 779 □AMD3100 □SFD-1 □Bicyclams □Aptamers
Membrane Disruption	Replication Inhibitors		
<ul style="list-style-type: none"> □Alkyl sulfates □Savvy (C31G) □Beta cyclodextrin 	<ul style="list-style-type: none"> □Tenofovir □TMC-120 □UC-781 □MIV-150 □MC1220 □C-731, 988 		

Current Clinical Candidates

□	PRO 2000: Gel	Ongoing	Phase 3
□	Truvada®: Oral†	Ongoing	Phase 3
□	Viread®: Oral†	Ongoing	Phase 3
□	Tenofovir: Gel†	Ongoing	Phase 2B
□	Dapivirine: Gel†	Ongoing	Phase ½
□	VivaGel®: Gel†	Ongoing	Phase ½
□	Acidform: Gel	Ongoing	Phase 1
□	Dapivirine: Ring	Ongoing	Phase 1
□	UC-781: Gel†	Ongoing	Phase 1
□	BufferGel®: Gel‡	Planned	Phase 3
□	Invisible Condom®: Gel	Planned	Phase 2/3
□	MIV-150+gel: Gel/Ring	Planned	Phase 1

† Multiple trials; ‡GC/chlamydia endpoints

IPM Portfolio

Compound	License	Type/Stage	Development Status
Dapivirine	Tibotec (2004)	NNRTI (reverse transcription)	In Phase I/II clinical trials (vaginal gel & ring)
M167, M872, M882 (DS001, 004, 005)	Merck (2005)	CCR5 blockers (attachment)	Pre-clinical (development on hold)
BMS793 (DS003)	BMS (2005)	gp120 binder (attachment)	Early pre-clinical
Tenofovir	Gilead (2006)	NRTI (reverse transcription)	Phase I PK (CONRAD & IPM) Phase IIB (CAPRISA, MTN)
Maraviroc	Pfizer (2008)	CCR5 blocker (attachment)	Pre-clinical
L'644 peptide (DS007)	Merck (2008)	gp41 binder (fusion)	Early pre-clinical



CONRAD Portfolio

- Projected timeline for initiation of milestone clinical studies:
 - UC781 PK – Q3 2009
 - UC781 6 mo expanded safety – Q2 2010? / MTN
 - UC781/TFV combination gel formulation initial PK & safety study – Q3 2010

- Other candidate microbicides, such as KP-n compounds (nucleoside derivatives), CCR5 blockers, INI, etc., are further back in the pipeline

Current MTN Portfolio

	Phase	Product (s)	08	09	10	11	12	13
HPTN-059	2	Tenofovir						
HPTN-035	2B	Pro-2000/BG						
MTN-001	1	TDF/Tenofovir						
MTN-002	1	Tenofovir						
MTN-003	2B	TVD/TDF/Tenofovir						
MTN-004	1	VivGel						
MTN-005	1	Placebo ring						
MTN-006	1	Tenofovir						
MTN-007	1	Tenofovir/HEC/N-9						
MTN-008	1	Tenofovir						
MTN-009	Resistance	N/A						
MTN-015	Seroconversion	N/A						
MTN-016	Pregnancy	N/A						

What Are the Opportunities?



MTN Opportunities

- New products
 - RTIs / entry inhibitors
- New formulations
 - Ring / film
- New routes of administration
 - Vaginal / oral / rectal / subcutaneous
- New populations
 - Adolescents / pregnant women / co-morbid conditions

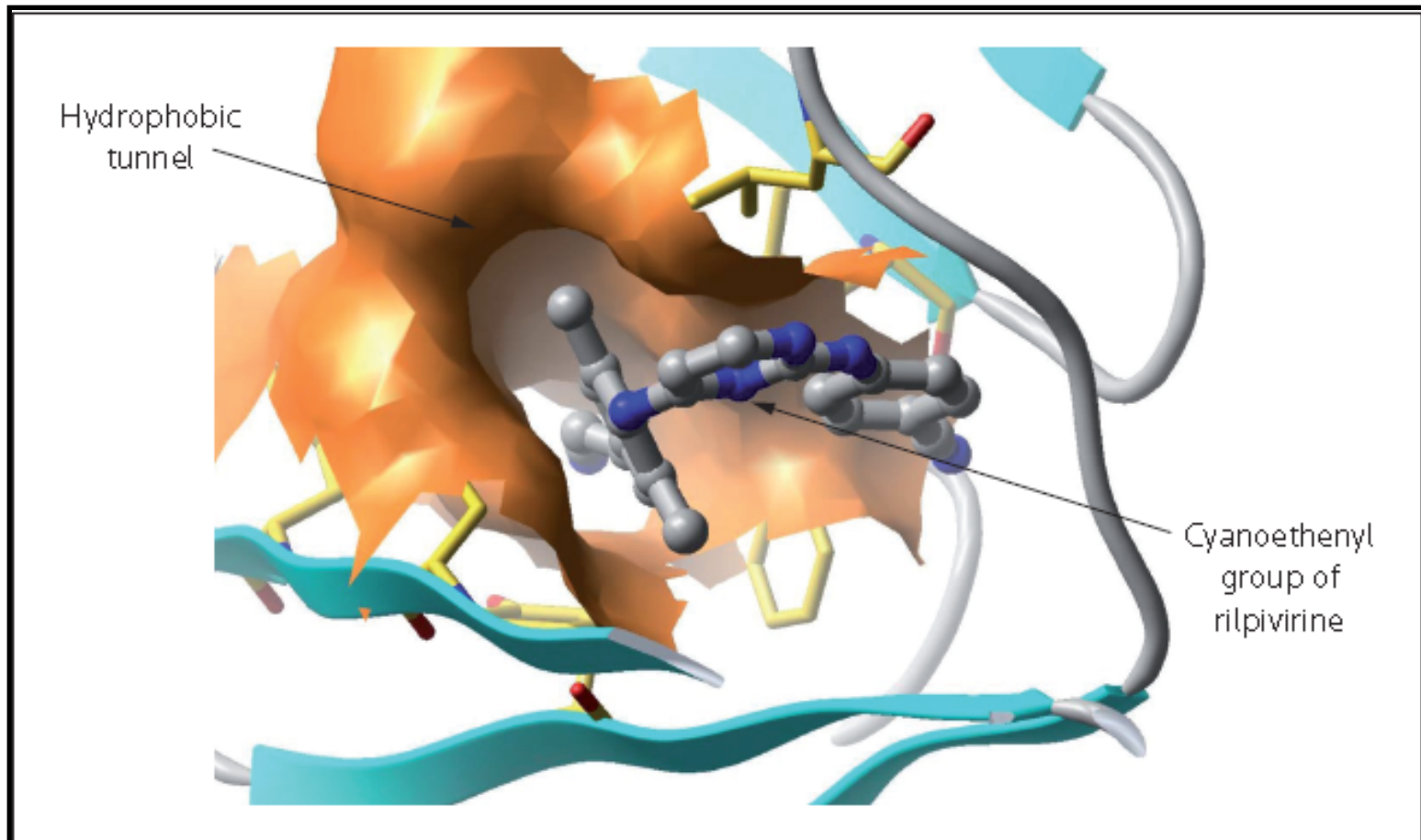


New Products

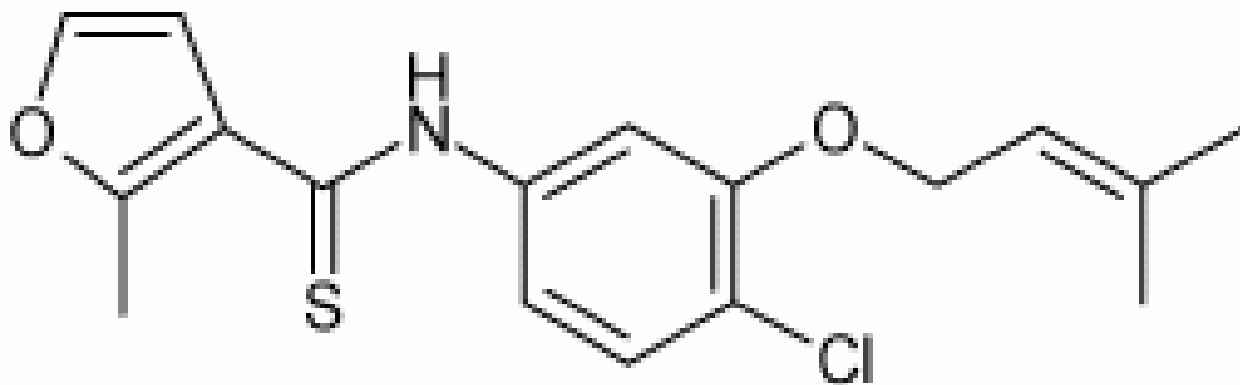
- Reverse transcriptase inhibitors
 - New formulation of UC781
 - TMC-278
- Fusion inhibitors
 - Maraviroc
 - RANTES analogues
 - Mapp66
 - VivaGel™
- Protease inhibitors
- Integrase inhibitors
- Other mechanisms
 - Glycerol monolaurate

Reverse Transcriptase Inhibitors

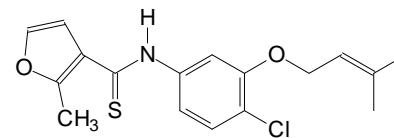
TMC-278



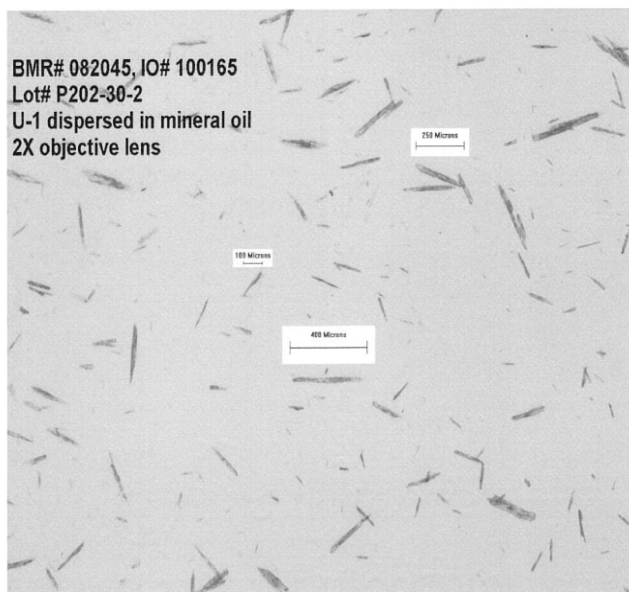
UC781



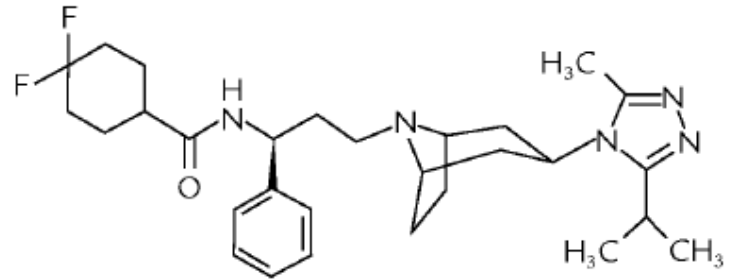
Micronized UC781



- Recently optimized synthetic procedure to increase yield and reduce number of steps (reduce cost)
- Micronized the drug substance (increase dissolution)



Maraviroc

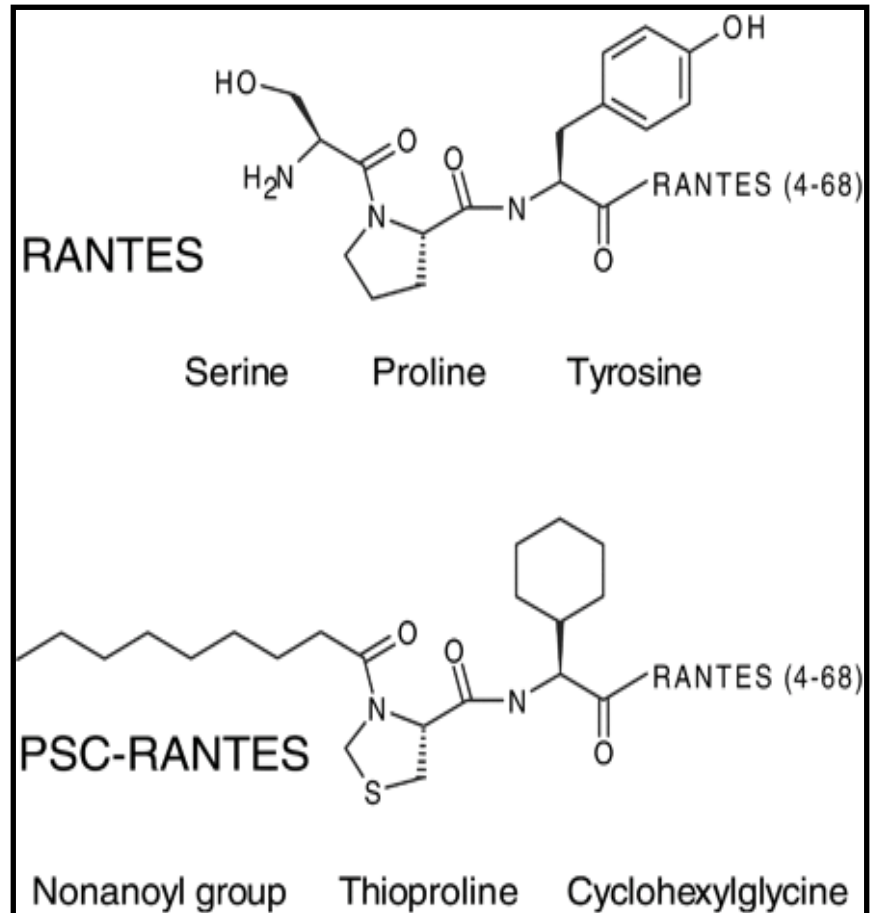


GlaxoSmithKline

Fusion Inhibitors

RANTES Analogues

- Human chemokine analogue
- Difficult synthetic pathway
- Potential for immunostimulatory activity
- 2nd generation candidates
 - 5P12-RANTES
 - 6P4-RANTES



mapp66





mapp66

- Anti-microbial topical agent composed of a humanized monoclonal against the human chemokine receptor CCR5 (aCCR5) and a human monoclonal antibody directed against HSV glycoprotein D

- **Proposed Indication:**
 - Reduce mucosal transmission of HSV/HIV

GMP production of mapp66 mAbs at KBP



mapp66 Non-coital Formulations

- Spray dry mapp66 to powder
- Initial mapp66 formulation as vaginal film or tablet

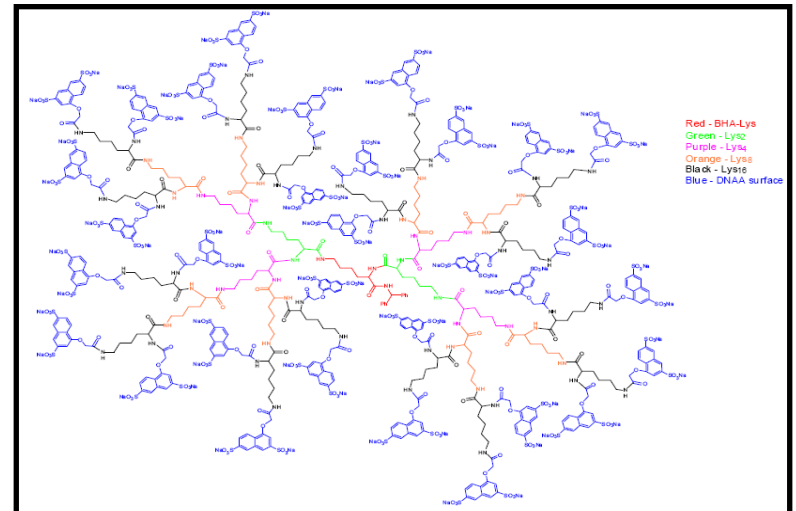


- Second generation mapp66 incorporated into one month ring (EVAc or Duet)



VivaGel™

- SPL7013:
 - Polysulphonated dendrimer
 - Formulated in Carbopol®[®], aqueous gel (VivaGel)
- Prevention of SHIV in macaques
 - 3% gel prevented infection in 5/6 animals,
 - 5% prevented 6/6
- Five clinical studies completed or planned:
 - Phase 1 vaginal safety x 4
 - Penile tolerance
 - Rectal Phase 1 (planned)

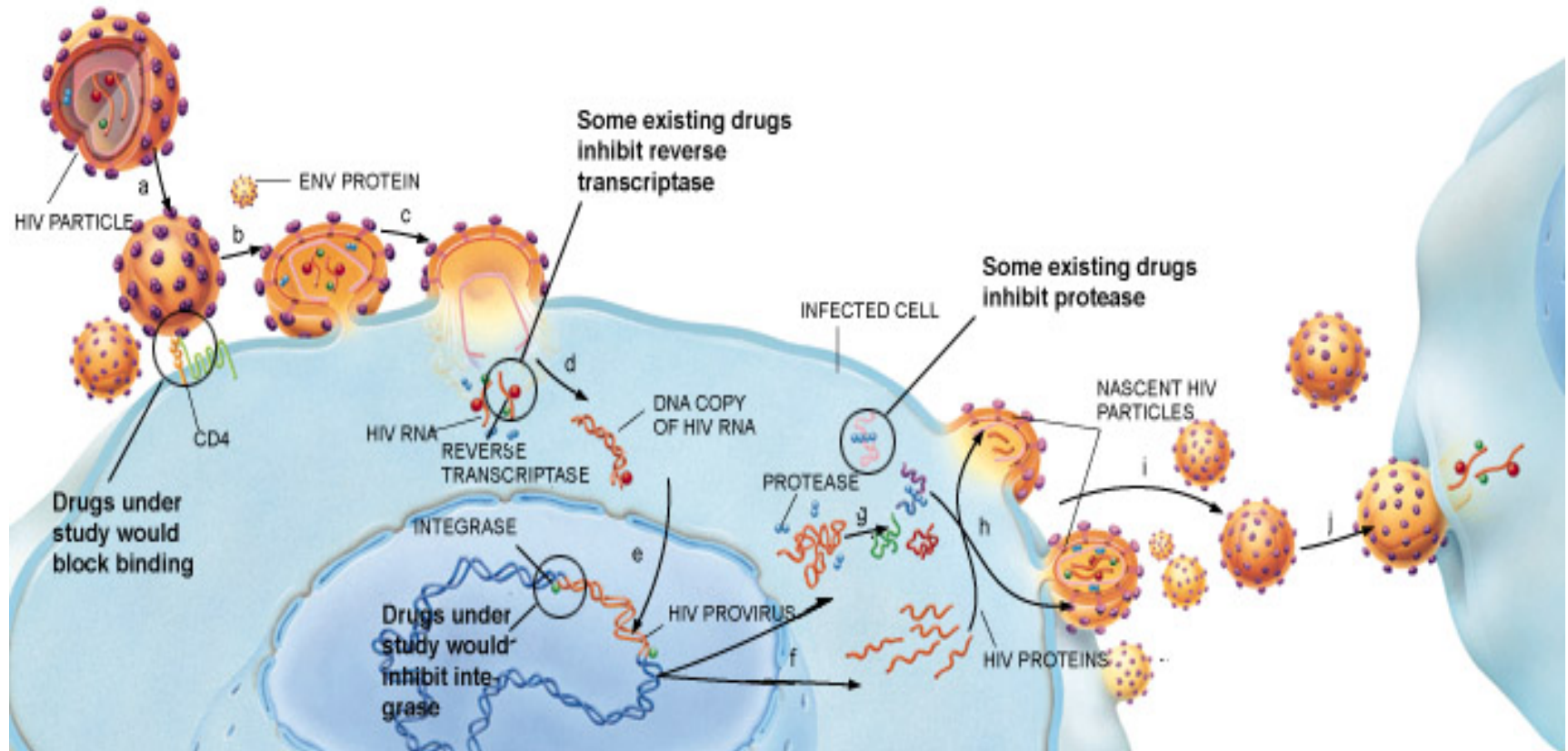


Protease & Integrase Inhibitors

Early Stage



Late Stage



Status of MTN Pipeline “Candidates”

Candidate	Status
TMC-278	On hold
UC781	Possible Phase 2
Maraviroc	Pfizer/GSK merger
RANTES analogues	?
mapp66	Preclinical evaluation ongoing
VivaGel™	Phase 1 program completed
Protease inhibitors	CTA in development with Merck
Integrase inhibitors	

New Formulations and Delivery Systems



New Formulations

- Vaginal
 - Gels
 - Ring
 - Film
- Rectal
 - Applicators
 - Gels

New Routes of Administration



New Routes of Administration

- Oral
 - Viread
 - Truvada
- Rectal
 - Tenofovir
 - VivaGel
 - UC781
 - TMC-120
- Subcutaneous
 - TMC-278

New Populations



New Populations

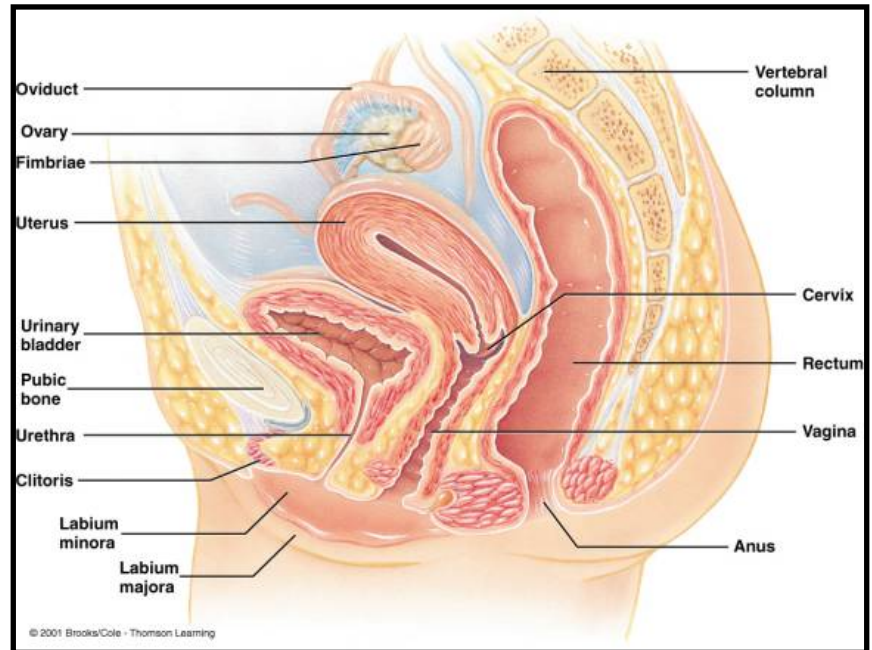
- Pregnant women
- Adolescents
- Men who have sex with men
- Individuals with chronic disease
 - Renal impairment
 - Hepatic impairment including chronic HBV
 - HIV infection

New Strategies

PK / Pathogenesis Studies

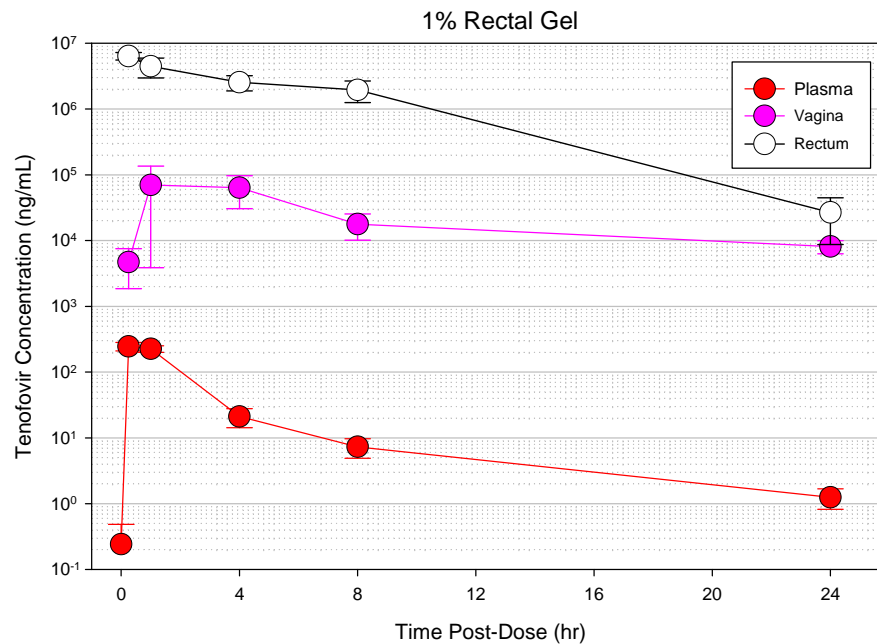
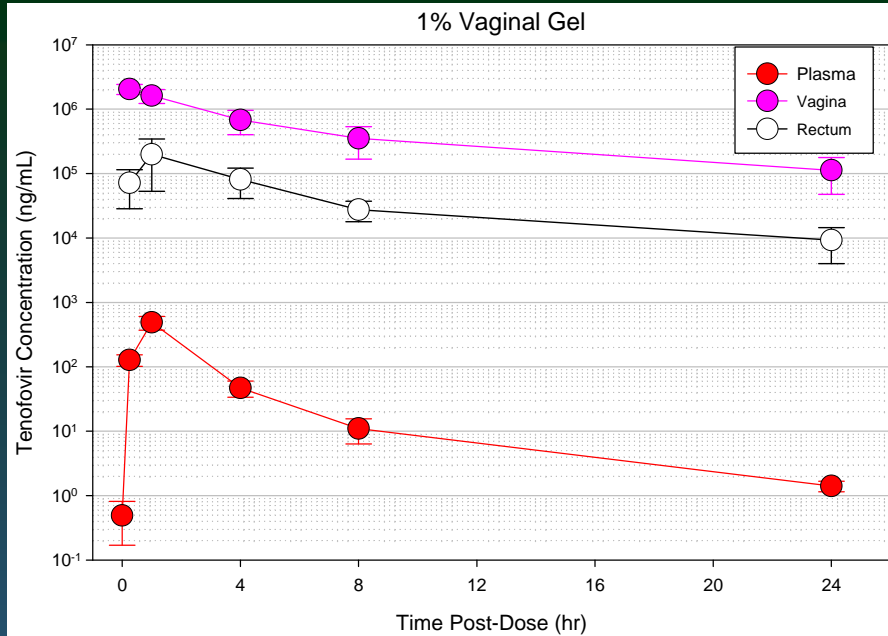
PK/Pathogenesis Studies

- Rectal PK following vaginal delivery of tenofovir gel
- IPM NHP studies show significant rectal drug exposure after vaginal delivery of 0.2, 1, and 5% tenofovir gel





1% Gel



Moving Out of the “Valley of Death”



Bridging Strategies

- NIH
 - DAIDS Integrated preclinical/clinical (IPCP) program
 - DAIDS / DMID Contract resources
 - R01 mechanism
 - SBIR
- External agencies
 - IPM
 - CONRAD
 - Bill and Melinda Gates Foundation
- Pharmaceutical company sponsorship



So What Can We Potentially
Do?



Key Areas for Development

- Development of new pipeline candidates
 - Phase 1 studies
- New populations
 - Adolescents
 - Pregnancy
 - Co-morbidity
- Rectal microbicide development
 - Phase 1 / 2 / 2B

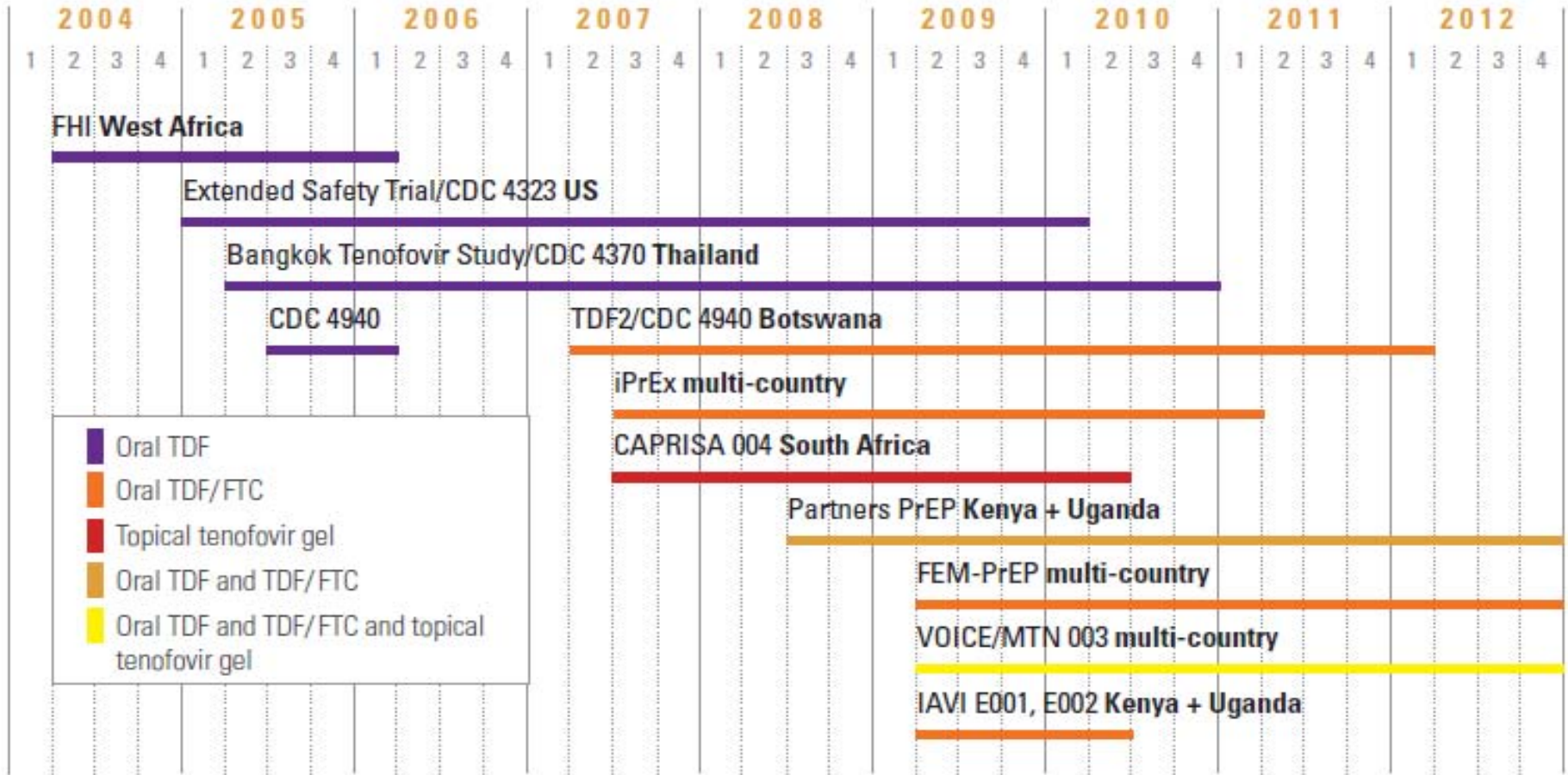
Actual & Potential MTN Portfolio

	Phase	Product (s)	10	11	12	13
MTN-003	2B	TVD/TDF/Tenofovir				
MTN-005	1	Placebo vaginal ring				
MTN-008	1	Tenofovir in P/L				
MTN-009	Resistance	N/A				
MTN-010	2	UC781 (V)				
MTN-011	2	Tenofovir (R)				
MTN-012	2	VivaGel™				
MTN-013	1	Protease inhibitor				
MTN-014	1	Integrase inhibitor				
MTN-015	Seroconversion	N/A				
MTN-016	Pregnancy register	N/A				

The Elephant in the Room



Life After an Efficacy Signal





Summary

- Significant preclinical / discovery microbicide portfolio
- Challenges in moving from preclinical to Phase 1
- Industry dialogue continues but is difficult
- Emerging data from ongoing PrEP studies will impact design of the MTN portfolio



Acknowledgements

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Thank You
