International Partnership for Microbicides

What The Future Holds For Next Generation Microbicides And Partnerships With Industry

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Beginnings of Microbicide Field

- Need for microbicides brought to light by leading women's advocates
- Zena Stein – 1990 article on "HIV Prevention: The Need for Methods Women Can Use"
- IWHC, WHO, WAND – 1991-92 meetings articulating need for microbicides
- IWHC & PopCouncil – Collaboration and creation of Women's Health Advocates on Microbicides
- ICRW – Key social behavioral research highlighted women's vulnerability and need for a female-initiated tool to prevent HIV
- GCM & AMD – Created in 1998, took advocacy on behalf of microbicide field to the global stage

Past Microbicide Efficacy Trials

Microbicide	Sponsors	Countries	Results / Reasons for Closure
Nonoxynol-9	NIH, AMFAR, FHI / Univ of Washington	Kenya	Sponge trial cancelled (1990) • More HIV+ in N-9 arm (not statistically significant)
	USAID, NIH / FHI	Cameroon	Film trial completed (1996) • No efficacy against HIV
	NIH / FHI	Kenya	Gel trial cancelled (1998) • Slow enrollment & follow up
	WHO, UNAIDS	Thailand, Benin, Cote d'Ivoire, SA	Gel trial completed (2000) • Trend towards harm
Savvy	USAID / FHI	Ghana	Gel trial cancelled (2005) • Low HIV incidence • No safety concerns
	USAID / FHI	Nigeria	Gel trial cancelled (2006) • Futility (no efficacy) • More HIV+ in Savvy arm (not statistically significant)

Past Microbicide Efficacy Trials (cont'd)

Microbicide	Sponsors	Countries	Results / Reasons for Closure
Cellulose Sulfate	Gates, USAID, Polydex / CONRAD	Benin, India, SA, Uganda, Zimbabwe	Gel trial cancelled (2007) • More HIV+ in CS arm (not statistically significant)
	USAID, Polydex / FHI	Nigeria	Gel trial cancelled (2007) • No safety concerns (precaution)
Carraguard	Gates, USAID / PopCouncil	South Africa	Gel trial completed (2007) • No efficacy against HIV • Good safety profile
PRO 2000 (2%)	UK MRC, DFID / MDP	SA, Tanzania, Uganda, Zambia	2% arm dropped (2008) • Futility (no efficacy) • Lower dose (0.5%) arm continues

Ongoing Microbicide Efficacy Trials: Early Generation

Product / Study	Phase	Mechanism of Action	Sponsor / Developer	Countries	Estimated Completion
BufferGel & PRO 2000 (0.5%) HPTN 035	2/2B	Defense Enhancer & Entry Inhibitor	NIAID / HPTN (MTN)	Malawi South Africa Zambia Zimbabwe USA	July 2008 Results 2009
PRO 2000 (0.5%) MDP 301	3	Entry Inhibitor	UK MRC, DFID / MDP	South Africa Tanzania Uganda Zambia	March 2009 Results 2009

Ongoing/Planned Microbicide Efficacy Trials: Next Generation

Product / Study	Phase	Mechanism of Action	Sponsor / Developer	Countries	Estimated Completion
Tenofovir CAPRISA 004	2B	ARV (NRTI)	DST (SA), USAID / CONRAD, CAPRISA	South Africa	Q2 2010 Results 2010
Tenofovir MTN 003/VOICE (Planned)	2B	ARV (NRTI)	NIAID / MTN	Malawi Uganda Zambia Zimbabwe South Africa	Q2 2011 Results 2011

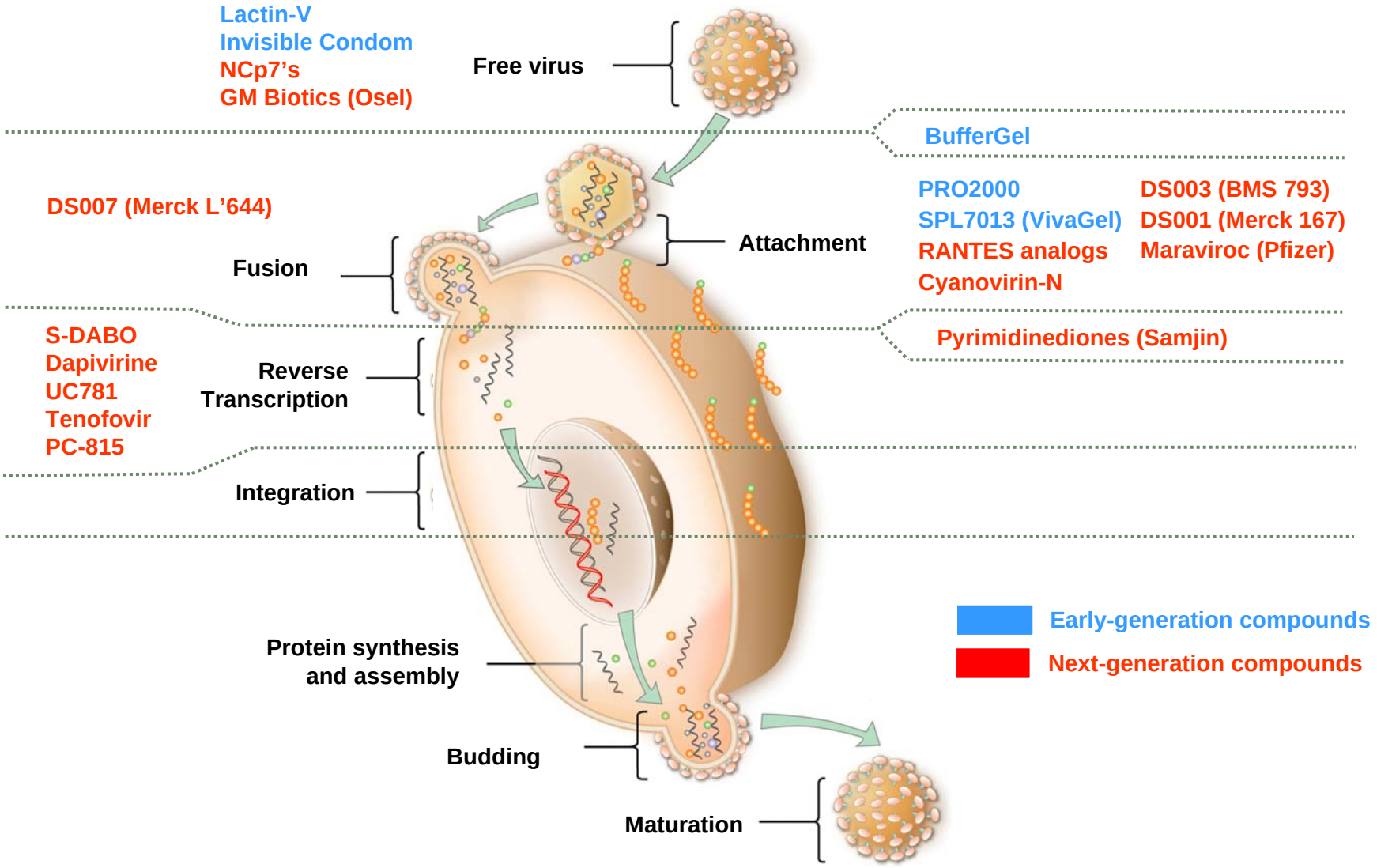
Lessons Learned from Prior Trials

Lessons learned	What is being done differently
Prioritization	• Adaptive design, multiple arms • Advance best product only
Safety	• Early looks for harm and ability to stop • Multiple data reviews during the trial
Adherence	• Longer acting formulations • Product acceptability studies • Daily contact with participants • Smart applicator
Incidence	• Epi studies conducted in advance
Futility	• Early stop if unlikely to show efficacy
Pregnancy	• Rigorous contraceptive requirements • Family planning, including female condoms
Trial locations	• Diversify in terms of countries and sites • Address co-enrollment concerns

Early & Next Generation Microbicides

Early Generation	Next Generation
• First microbicides tested, some still in efficacy trials	• Newer products in different stages of preclinical and clinical research
• Not HIV specific	• Specific to HIV (ARV-based)
• Gel formulations	• Various forms: gel, ring, film, tablet
• To be applied vaginally within a few hours before sex	• Longer duration of action: daily gels, monthly rings, etc.
• No concern about potential resistance	• ARV resistance is a possible issue that needs to be investigated

Microbicides in Product Development



Partnerships with Industry

Compound	License	Year	Type/Stage	Development Status
Dapivirine	Tibotec	2004	NNRTI	Phase I/II (vaginal gel, ring)
M167, M872, M882	Merck	2005	CCR5 blockers	Pre-clinical
BMS793	BMS	2005	gp120 binder	Early pre-clinical
Tenofovir	Gilead	2006	NRTI	Phase I PK (CONRAD / IPM) Phase IIB (CONRAD / CAPRISA) Phase IIB (MTN, planned)
Maraviroc	Pfizer	2008	CCR5 blocker	Pre-clinical
L'644 peptide	Merck	2008	gp41 binder	Early pre-clinical

Intellectual Property Rights

- Non-exclusive royalty-free licenses to develop, manufacture and distribute antiviral compounds as microbicides in developing countries
- Ongoing technical support from industry
  - Drug synthesis
  - Site evaluation
  - New compounds

Dapivirine Ring & Gel

Study	Design	Countries	Study Results
IPM 001, IPM 008	7 days 25 or 200 mg N=25	Belgium	• Reservoir ring safe and well tolerated • High drug levels (> 1000 x EC50) well distributed in vaginal tissues & fluids • Low levels in plasma (<50 pg/mL)
IPM 018	28 days 25 mg N=24	Belgium	• Both reservoir & matrix rings safe and well tolerated • High drug levels (> 4 logs x EC50), significantly more drug with matrix • Low levels in plasma (<2 ng/mL)

Study	Design	Countries	Study Results
IPM 003, IPM 005B	42 days 2.5 ml N=148	Rwanda South Africa Tanzania	• Safe and well tolerated • No drug-related SAEs
IPM 004	10 days 2.5 ml N=18	South Africa	• Safe and well tolerated • No drug-related SAEs • PK data supports once-daily use

Product Acceptability Studies

- Placebo gel formulations
  - Completed 2006
  - Kenya, South Africa, Zambia

- Placebo vaginal ring
  - South Africa, Tanzania – ongoing
  - Kenya – follow up

- Placebo vaginal tablet, film, soft gel capsule
  - Planned 2008-09
  - Burkina, Mozambique, Tanzania, Zambia

Microbicide Donors

- Belgium
- Canada
- Denmark
- France
- Germany
- Ireland
- Netherlands
- Norway
- South Africa
- Sweden
- United Kingdom
- USA
- European Commission
- World Bank
- UNFPA
- Rockefeller Foundation
- Gates Foundation

What More Could Industry Do?

- $$$, €€€, £££, DKK …
- Linkages for formulations development
- Long-term seconded technical expertise
- Site development support in overlapping areas
- Support for access:
  - Sharing experience in resource limited settings
  - Product forecasting tools & procurement management
- Guidance on:
  - Relations with regulatory bodies for product approval
  - Issues of product liability and pharmacovigilance
  - Selecting outside technical expertise and vendors
  - Managing organizational growth