Microbicide Product Development and Implications

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## Comprehensive Approaches to HIV/AIDS

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Time of Exposure</th>
<th>Treatment and Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior to Exposure</strong></td>
<td><strong>Male and female condoms</strong></td>
<td><strong>Anti-retroviral therapies</strong></td>
</tr>
<tr>
<td>Vaccines Pre-exposure prophylaxis Male circumcision HSV suppression Cervical barriers Behavior change</td>
<td></td>
<td>Opportunistic infection therapies</td>
</tr>
<tr>
<td></td>
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<td>Basic care</td>
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</tbody>
</table>

**Microbicides**
The time to act is short

HIV

Afferent lymphatics

Increased virus replication and spread

Langerhans Cells

Sub-mucosal DCs

Afferent lymphatics

Draining lymphoid tissue

minutes

hours
Activity and safety in at risk populations

Ectopy

Trichomoniasis

HSV
## The microbicide pipeline

<table>
<thead>
<tr>
<th>Defense Enhancers</th>
<th>Non specific Entry Inhibitors</th>
<th>Specific entry inhibitors</th>
<th>ARVs</th>
<th>Virus binders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidform™ Lime Juice Lactobacillus BufferGel™</td>
<td>Cellulose acetate VivaGel™ PRO 2000 Carraguard Cellulose Sulfate Polystyrene sulfonate SAMMA K5-N OS SP</td>
<td>CCR5 antagonists (CMPD167, PSC-RANTES) gp41 inhibitors (CL52, T1249) CADA (CD4 suppressor)</td>
<td>NRTI (PMPA) NNRTI (UC781, TMC 120, MIV150, DABO)</td>
<td>Lectins (CV-N, HHA) BMS 806 CD4 mini proteins Mabs PRO542</td>
</tr>
<tr>
<td>GMOs</td>
<td>Others</td>
<td>Specific entry inhibitors</td>
<td>Combinations</td>
<td>Membrane-disruptive agents</td>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C31G</td>
</tr>
</tbody>
</table>
Targeting the virus

**CD4-binding site**
- CD4-IgG2 (PRO-542)
- BMS-806
- mAb b12

**Membrane-active agents**
- Nonoxynol-9
- C31G
- Cyclodextrins

**Glycan residues**
- mAb 2G12
- Cyanovirin-N

**Host cell-surface proteins** (e.g. MHC-II, LFA-1)

**Poylanions**
- PRO-2000
- Dextrin-2-sulphate
- Cellulose sulphate
- Carageenan
- SAMMA
- Cellulose acetate phthalate

**gp41 ligands**
- T-20
- T-1249
- mAbs 2F5, 4E10

**Env**

**gp120**

**V3**

**V1/2**
1% gadolinium 1:100 in a sterile system with Dextrin sulphate gel, 2hrs post application (C. Lacey, Imperial College)

Compound must be present at the time of viral exposure

Cervix  
Vagina  
Vulva  
Anus
Targeting cells

**a Attachment**
- DC-SIGN
- HSPG
- LFA-1
- ICAM-1

**b CD4 binding**
- CD4
- CD4 mAbs (e.g. TNX-355)

**c Co-receptor binding**
- Co-receptor

**d Hairpin formation and membrane fusion**
- Modified chemokines (e.g. PSC-RANTES)
- Small-molecule inhibitors (e.g. SCH-C)
- Co-receptor-specific mAbs (e.g. PA14)

Ligands for DC-SIGN (e.g. anti-DC-SIGN mAbs, mannan), adhesion molecules (e.g. anti-ICAM-1 mAb) or HSPGs
Target cells must be protected at the time of viral exposure.

1% gadolinium 1:100 in a sterile system with Dextrin sulphate gel, 2hrs post application (C. Lacey, Imperial College)
First generation microbicides

(PRO2000, Carraguard, Cellulose Sulphate, Buffer gel,)

Advantages
• Safe √ Cheap √ User-friendly √ Broad activity √

Disadvantages
• No proof of concept in animal models (R5)
• Broad activity may reduce potency
• Coitally dependent - high compliance burden
First generation polyanions work best against X4 virus

PRO2000  Carraguard  Cellulose  Sulphate

Most HIV transmission is mediated by R5 virus

Shattock | 2003

Fletcher et al, Retrovirology 2006 ;3(1):46
PRO2000 blocks HIV-1 infection of cervical tissue

Retrovirology. 2006;3(1):46
ARV microbicides
(TMC-120, UC-781, MIV-150, PMPA)

Advantages
• Safe ✓ Cheap ✓ Highly active ✓ Could be formulated for sustained release.

Disadvantages
• Potential for resistance
• Lack of activity against other STDs
(both could be overcome with combination products)

Require proof of concept studies in animal models
PMPA is active against both localized infection and dissemination pathways

Cervix p24

Cervix: provirus

DC-dissemination
NNRTIs demonstrates significant memory effects

Cervix p24

Cervix: provirus

DC-dissemination

TMC-120

Also demonstrated for UC781 (J Virol 2005. 79:11179-86)
Entry inhibitor microbicides

(CMPD-167, BMS-806, PSC-RANTES)

Advantages
• **Highly active ✓** Could be formulated for sustained release.

Disadvantages
• **Lack of activity against X4 virus**
• **Lack of activity against other STDs**

(both could be overcome with combination products)
Only limited animal model data exist for current microbicide candidates

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>protection</th>
<th>virus</th>
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</thead>
<tbody>
<tr>
<td><strong>Virus binders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAb b12</td>
<td>5 mg/ml</td>
<td>1/5</td>
<td>R5</td>
</tr>
<tr>
<td>CV-N</td>
<td>5 mg/ml</td>
<td>0/5</td>
<td>X4</td>
</tr>
<tr>
<td>BMS-806</td>
<td>3 mg/ml</td>
<td>2/8</td>
<td>R5</td>
</tr>
<tr>
<td><strong>Entry inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAP</td>
<td>100 mg/ml</td>
<td>3/10</td>
<td>R5</td>
</tr>
<tr>
<td>PRO-2000</td>
<td>5 mg/ml</td>
<td>0/7</td>
<td>X4</td>
</tr>
<tr>
<td>CMPD 167</td>
<td>5 mg/ml</td>
<td>2/10</td>
<td>R5</td>
</tr>
<tr>
<td>PSC-RANTES</td>
<td>5 mg/ml</td>
<td>0/10</td>
<td>R5</td>
</tr>
</tbody>
</table>

Need for expanded animal studies to allow side by side comparison of compounds and formulations
Combinations have several advantages over single agents for microbicides, just as for therapy

- Combinations may permit the simultaneous blockade of more than one possible transmission pathway increasing efficacy.

- Synergy between some inhibitors may reduce the concentrations needed for effective inhibition and increase potency.

- An increased breadth of coverage against circulating HIV-1 strains and other STDs may be provided by combinations.

- Combinations may reduce the probability of transmission of variants that are resistant to any one inhibitor.

- May reduce viral shedding in those unaware of their status

**Disadvantages:**

Unclear regulatory pathway, complex trial design, increased potential for toxicity, cross company/institutional agreements
Single entry inhibitors and combinations protect monkeys against vaginal challenge by SHIV-162P3

9/9 control animals given placebo gel were infected.

21/28 (75%) of animals given one inhibitor were protected \( (p = 0.000092) \).

16/20 (80%) of animals given two inhibitors were protected \( (p = 0.000071) \).

3/3 (100%) of animals given three inhibitors were protected \( (p = 0.0045) \).

Overall, 40 of 51 (78%) inhibitor recipients were protected.

John Moore, Toronto 2006
Rectal microbicides?

AIDS. 2006;20:1237-45.


FASEB J. 2006; 20:356-8
## How will they be used

<table>
<thead>
<tr>
<th></th>
<th>Coitally dependent gel</th>
<th>Once-a-day gel</th>
<th>30 day ring</th>
<th>90 day ring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units/year</td>
<td>100</td>
<td>365</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>$ cost/unit</td>
<td>0.6</td>
<td>0.6</td>
<td>5-10</td>
<td>5-10</td>
</tr>
<tr>
<td>$ cost/year</td>
<td>60</td>
<td>219</td>
<td>60-120</td>
<td>20-40</td>
</tr>
</tbody>
</table>

(based on phase 3 unit costs - source: IPM)
Future Direction

• **Rational drug development strategy**
  (product selection/rationalization)

• **Access to animal models/development of new models**
  Strategies to provide sustained delivery (reduction of compliance burden)

• **Development of potent combinations**
  (increased potency, decreased resistance)

• **Strategies to enhance innate protection**

• **Integrating with other prevention strategies**
  (vaccines, PreP, HSV Suppression, cervical barriers, circumcision)
An international partnership

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