



***THE MICROBICIDE RESEARCH AND
DEVELOPMENT “PIPELINE”:
A STATUS REPORT***

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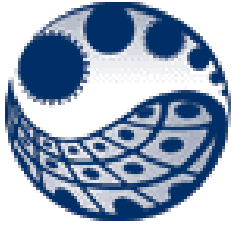
Director, Alliance for Microbicide Development

Microbicides 2002

Antwerp, Belgium--May 13, 2002

Email: pharriso@aol.com

Alliance for Microbicide Development

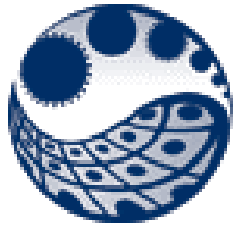


who is doing the work?

- **25 biopharmaceutical companies**
- **38 non-profit research entities**
- **5 public-sector entities worldwide**
- **36 supportive research entities**

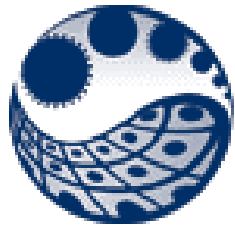
they are working on:

- **at least 52 product leads**
- **2+ different delivery devices**
- **1+ special formulations**

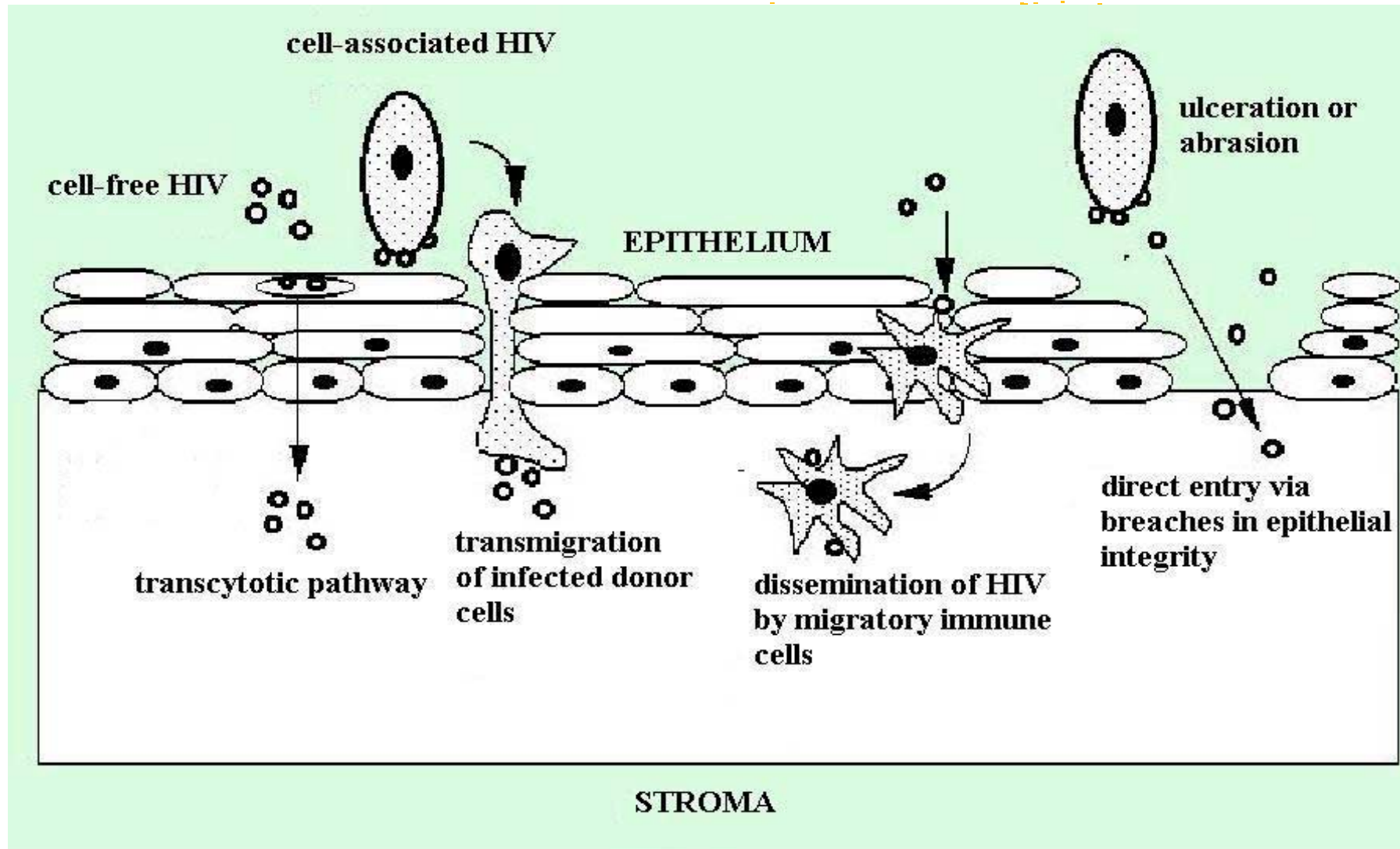


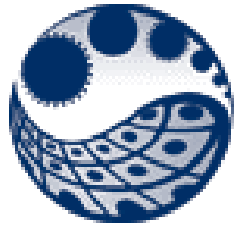
where are they/we?

Phase 3	1	
Phase 2/3	2	
Phase 2	2	
Phase 1	9	
<i>total in clinical stages:</i>		<i>14</i>
some animal data	20?	
some <i>in vitro</i> data	18?	
<i>total in preclinical stages:</i>		<i>38?</i>
<i>total products in development:</i>		<i>52?</i>

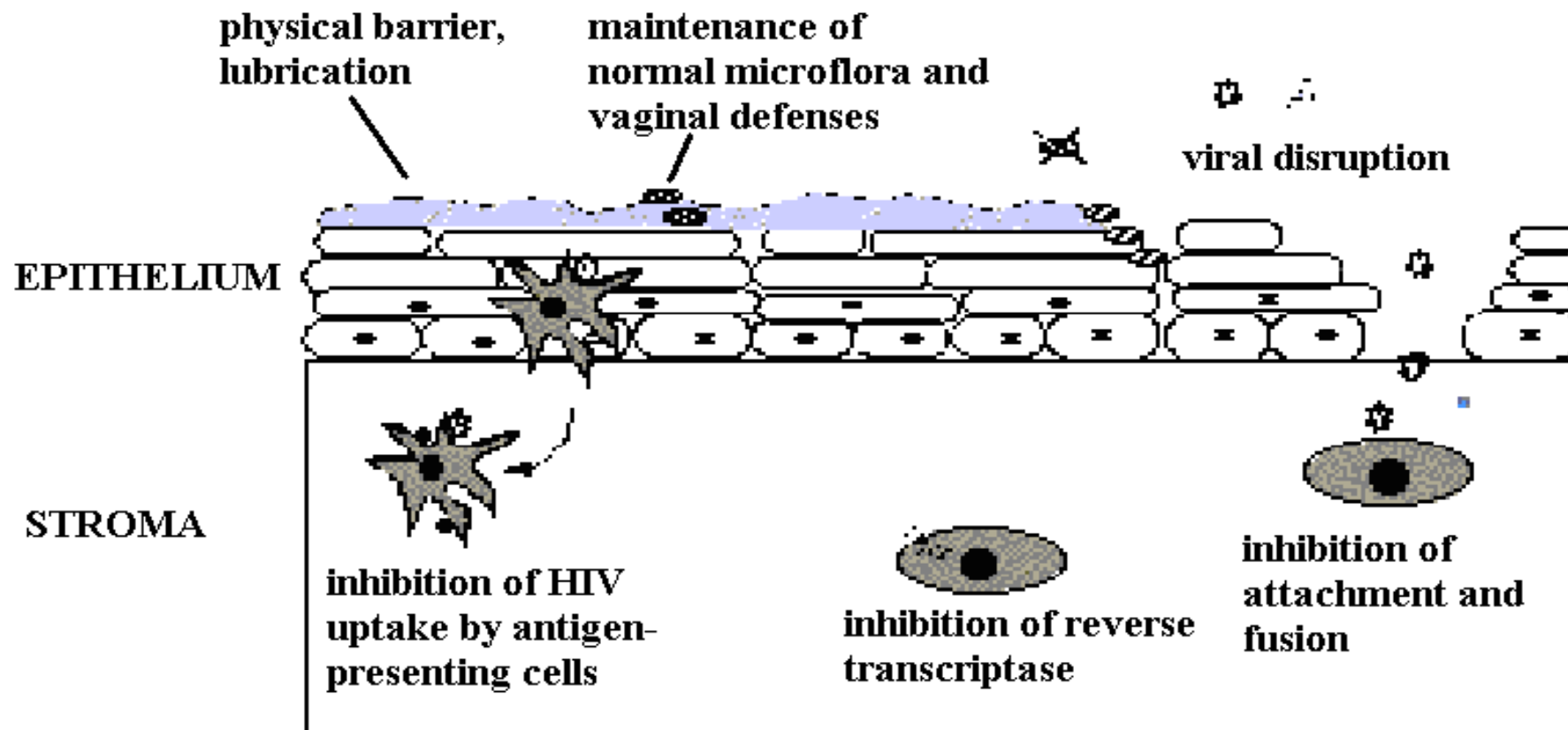


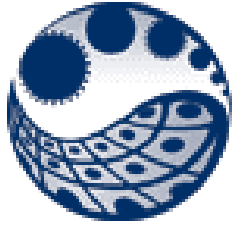
mechanisms of viral infection





potential mechanisms of action for an HIV microbicide

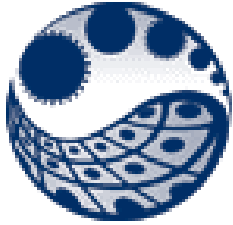




microbicides in development (by mechanism of action)

acid buffers/vaginal defense enhancers [“8”]

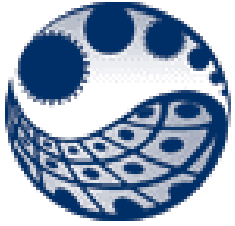
- ➔ **antibiotic peptides (protegrins, retrocyclin, Vena-Gel)**
- ➔ **buffered gels (Acidform, BufferGel)**
- ➔ **lactobacillus-containing compounds (engineered lactobacillus, lactobacillus suppository)**
- ➔ **monoclonal antibodies (“plantibodies”)**
- ➔ **topical estrogens**



microbicides in development (by primary mechanism of action)

**surfactants [“8”]
(non-specific
surface-active agents)
*kill/inactivate virus/
bacteria/sperm
(disrupt membrane/
envelope [e.g., pore
formation,
agglutination,
coating cell/virus])***

- benzalkonium chloride
- C31G/Savvy
- inorganic oxidants
- octoxnol-9/(Geda Plus)
- octyl glycerol/milk lipids
- polybiguanides
- sodium dodecyl sulphate
- Z14/acyl-carnitine analog



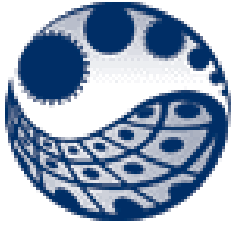
microbicides in development (by primary mechanism of action)

**adsorption inhibitors
[“7”]**

**(primarily sulfated &
other charged
polymers)**

*inhibit first steps in life cycle
of sexually-transmitted
viral pathogens/entry into
mucosal cells*

- Carraguard (PC-115)
- cellulose sulfate (PS)
- dimandelic acid ether (SAMMA)
- Emmelle (dextrin-2-sulfate)
- PRO-2000 (naphthalene sulfonate polymer)
- polystyrene sulfonate (PSS)
- polymethylene hydroquinone sulfonate (PMHS)
- sulfonated hesperidin

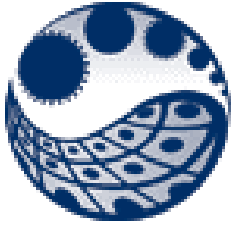


microbicides in development (by primary mechanism of action)

entry & fusion inhibitors [“11”]

*prevent entry/fusion
between membrane of
invading pathogen and
host cell*

- AOP-Rantes
- betacyclodextrin
- CCR-5 inhibitors
- chimeric protein with soluble CD4 (CD4-17b)
- CXCR4
- cyanovirin-N
- liposome-generated artificial membranes
- SPL7013
- thrombospondin-1 (TSP1)-derived peptides
- WHI-07 (AZT derivative)

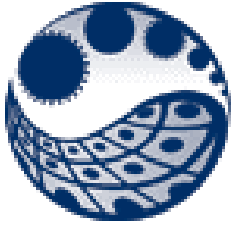


microbicides in development (by primary mechanism of action)

replication

inhibitors [“3”]

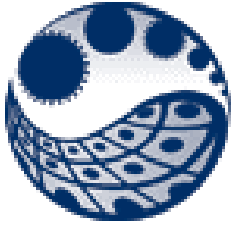
- inhibit postfusion activity/replication* • non-nucleoside reverse transcriptase inhibitors (DapivirineTM, UC-781, others)
- nucleotide reverse transcriptase inhibitors (tenofovir/PMPA)



microbicides in development (by primary mechanism of action)

multiple mechanisms [“4”]

- **antiviral proteins (MAP30 and GAP31)**
- **cellulose acetate phthalate/CAP**
- **monocaprin- and PAVAS-containing hydrogel**



microbicides in development (by primary mechanism of action)

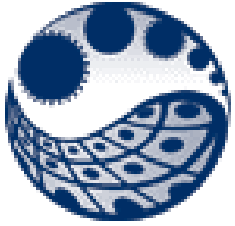
Uncharacterized/Unknown Mechanism(s) [“7”]

Natural Products

- Praneem polyherbal vaginal tablet
- pokeweed antiviral protein (PAP)

Other

- aldrithiol-2 (AT-2)
- Doxovir-M (cobalt-containing complex)
- porphyrins and protoporphyrins
- synthetic membrane transit peptides
- zinc gluconate gel (Zn-G-Gel™)



microbicides in development

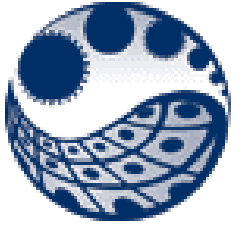
(by primary mechanism of action)

devices [“6”]

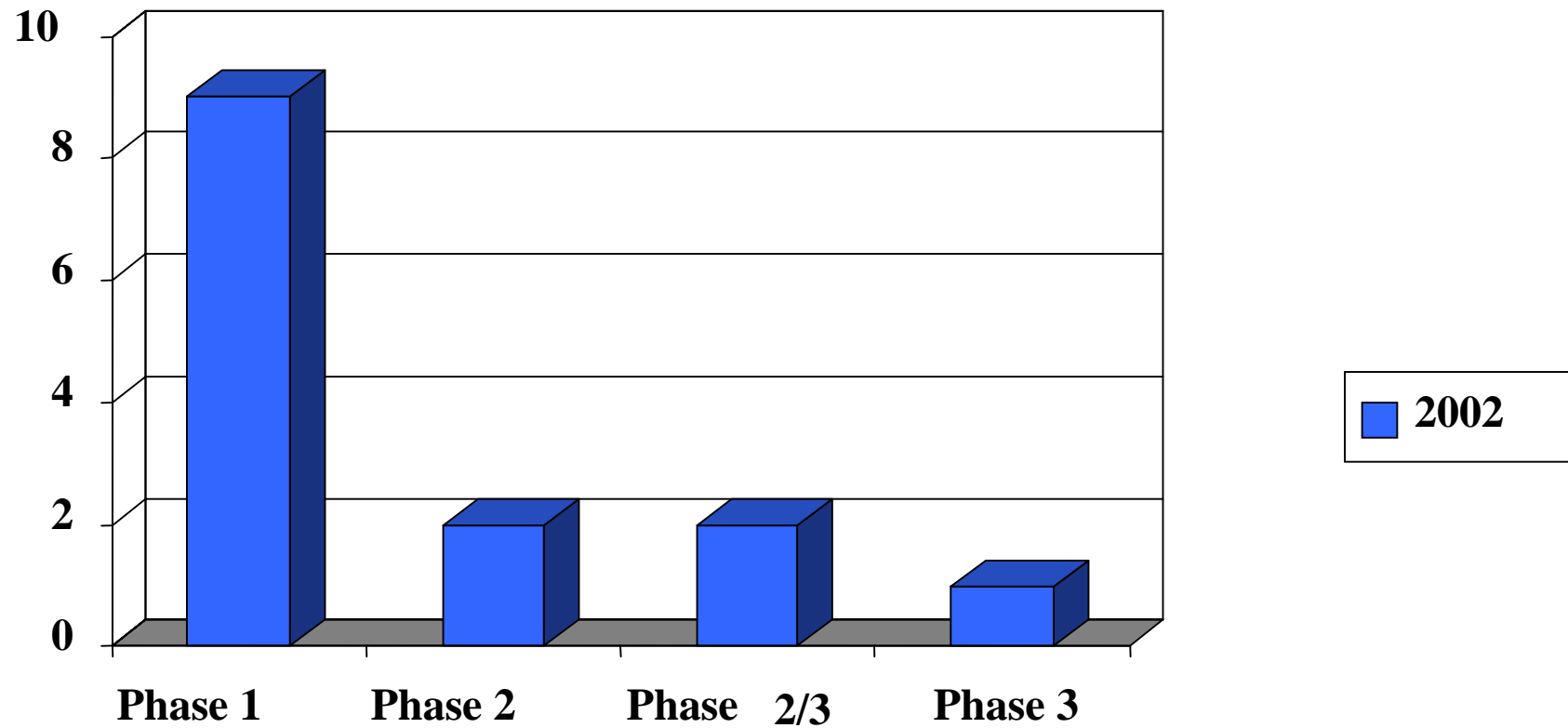
- **BufferCup**
- **FemCapTM (cervical cap)**
- **OvesTM (cervical cap)**
- **SILCS intravaginal barrier**
- **Supermatic Foamer System 96**
- **vaginal ring**

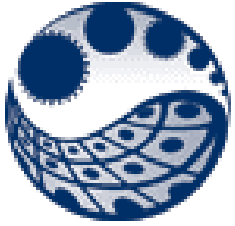
formulations [“1”]

- **PharmaDurTM**



microbicides in clinical trials, may 2002

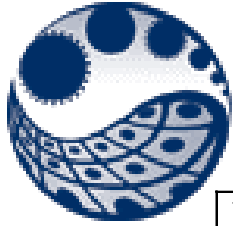




the phases in detail

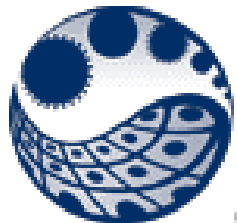
	Number of Participants	Length	Purpose
Phase 1	20-100	Several months	Safety
Phase 2	~200 (couples)	6 months to 1 year	Expanded safety
Phase 3	3000-5000	1-4 years	Effectiveness

+ Phase “2/3”



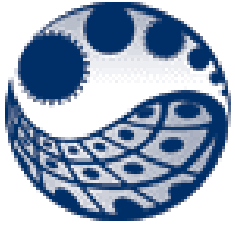
products in clinical trials (N=14, 2002)

Product	Phase 1	Phase 2	Phase 2/3	Contraceptive Efficacy	Phase 3
Acid Buffers/Enhancers of Vaginal Defenses					
Acidform™	GMP				
Benzalkonium Chloride	Biofem				
BufferGel™			HPTN Reprotect	NICHD Reprotect	
Invisible Condom™	Laval				
Lactin Vaginal Capsule		NIAID			
Praneem	Institute of Research in Reproduction				
SPL7013	Starpharma				
Surfactants					
Savvy (C31G)	GMP Biosyn			NICHD Biosyn	
Entry Inhibitors					
Carraguard™					Pop Council CDC
Cellulose Sulfate (CS)	GMP				
Emmelle™ Dextrin-2 Sulfate		MRC ITM			
Polystyrene sulfonate	GMP				
PRO 2000			HPTN Interneuron		
Replication Inhibitors					
Topical PMPA	HPTN Gilead				



clinical trial sites





microbicide clinical trial sites

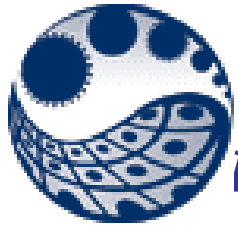
Acidform: *Phase 1-* Brazil, USA (Baltimore, Cincinnati, Houston, Pittsburgh)

BufferGel: *Phase 1-* USA (Los Angeles, Seattle)
Phase 2/3- India, Malawi, South Africa, Tanzania, Zimbabwe, USA (California)

C31G (Savvy): *Phase 1-* USA (Pittsburgh, Philadelphia)

Carraguard: *Phase 1-* South Africa, Thailand, USA (NYC)
Phase 2- South Africa, Thailand
Phase 3- Botswana(?), South Africa

Cellulose Sulfate: *Phase 1-* India, Nigeria, Uganda
USA (Los Angeles, NYC, Norfolk, Philadelphia, Pittsburgh, Providence)



microbicide clinical trial sites (continued)

Emmelle/Dextrin Sulfate: *Phase 1*- Belgium, UK

Lactin Vaginal Capsule: *Phase 2*- USA (Pittsburgh, Seattle)

PMPA (Topical): *Phase 1*- USA (NYC, Philadelphia, Providence)

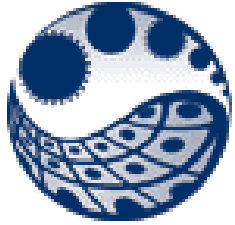
Polystyrene Sulfonate/PSS: *Phase 1*- USA (Norfolk, Pittsburgh)

PRO 2000 : *Phase 1*- India, USA (Houston, Madison)

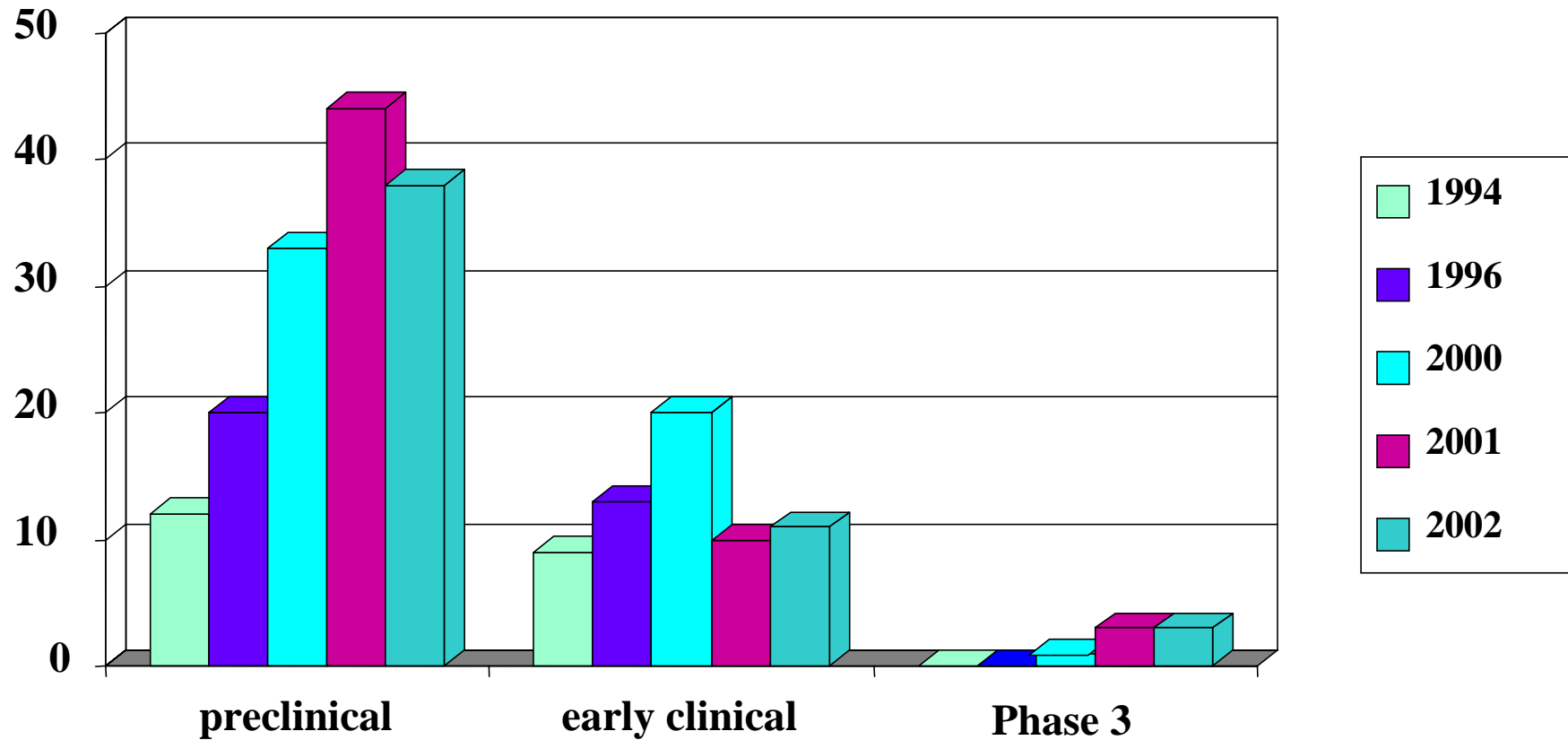
Phase 2- Côte d'Ivoire, Uganda

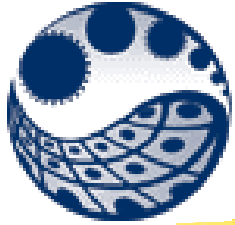
Phase 2/3- India, Malawi, South Africa,
Tanzania, Zimbabwe

SPL7013: *Phase I* - USA (Miami)



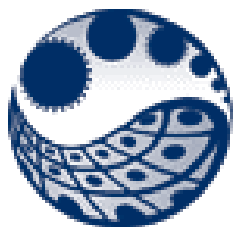
trends in microbicide development





changes in the microbicide pipeline, 1996, early 2001, early 2002

Category	1996	early 2001	early 2002
barriers			only 1 (Reality) on the US mkt. + Oves in Eur.
peptides	2	3(magainins?)	2 (preclinical)
acidic gels	2	2	2 (in clinical)
lactobacillus	basic work	in phase II	+ basis/platform? for CD-4 and cyanovirin-expressing lactobacillus
monoclonal antibodies	1	2	2+
topical estrogens		1	1



changes in the microbicide pipeline, 1996, early 2001, early 2002

Category	1996	early 2001	early 2002
oxidants		2	2?
surfactants	17	12	8
sulfated polymers	7	7	8
entry& fusion inhibitors	4	5-6	12
NNRTIs	1	2	3
nucleotide inhibitors	2	1	1
multiple mechanisms	2	2	3
uncharacterized/natural	2	2	3
uncharacterized/other	1	1	5
formulations	3	3	2
