MICROBICIDE CANDIDATES IN PRECLINICAL DEVELOPMENT AS OF OCTOBER 2009*

ALLIANCE FOR MICROBICIDE DEVELOPMENT

ADVANCED PRECLINICAL†

Candidate	*Mechanism of Action*	*Developer/Researcher/Sponsor*	*Additional Information+*
CAP	Combination (2 or more mechanisms of action)	The New York Blood Center, NIAID	*Soluble CAP inhibits HIV-1 entry/fusion by binding to HIV-1 gp120, interfering with its interaction with co-receptor CCR5 or CXCR4. Both soluble and micronised CAP (which adsorbs HIV) induce "dead-end" gp41 six-helix bundles.*
Cyanovirin-N (CV-N)	Entry/fusion inhibitor, Vaginal defense enhancer	NIH, Osel Inc., University of Pittsburgh	*Also known as MucoCept, in NHP Mode*
D-peptides	Entry/fusion inhibitor	NIH, University of Utah School of Medicine (M Kay)	*D-peptides have broad antiviral activity (clades A-G) using PBMC target cells. Pharmacokinetic studies are now underway. Currently undergoing preclinical evaluation in NIAID's Topical Microbicide Screening Algorithm.*
5P12- RANTES	Entry/fusion inhibitor	The Mintaka Foundation for Medical Research	*A fully recombinant analogue of PSC-RANTES with equivalent potency in vitro and equivalent efficacy in the macaque vaginal challenge model. Lower product costs and better safety profile (no CCR5 signaling) than PSC-RANTES.*
mapp66	Combination of antibodies, neutralization	Mapp Biopharmaceutical, Inc.	*mAbs produced in Nicotiana; one mAb blocks HIV binding to CCR5 receptor, one mAb binds to gpD on HSV*
Nisin	Combination	National Institute for Research on Reproductive Health (Reddy KVR)	*No anti-HIV activity but is effective against various sexually transmitted pathogens. Advanced preclinical studies in rabbits suggest is safe and effective as a spermicide.*
Octylglycerol Gel	Surfactant	NY State Institute for Basic Research, Magee-Women's Research Institute: University of Pittsburgh (CE Isaacs, L Rohan, S Hillier)	*Monkey efficacy and toxicity studies are presently underway at University of Washington (D Patton)*
Opuntia spp (Osp)	Entry/fusion inhibitor, Replication inhibitor	CIDEPLAN, SELADIS (R Carvajal, K Terrazas, S Zambrana, P Terceros)	
PEHMB	Entry/fusion inhibitor	Drexel University College of Medicine, Novaflux Biosciences, Inc.	*Working toward further defining one or two additional mechanisms of antiviral activity*
Polycarboxylated aryl oligomer, poly[1,4-phenylene-(1-carboxyl) methylene] **(PPCM)**	Entry/fusion inhibitor	Albert Einstein College of Medicine (AECOM), TOPCAD/Rush University, YASO	*In vitro and mechanistic studies completed, formulation fully protective in murine herpes model; contraceptive*
Retrocyclins	Entry/fusion inhibitor	NIH, UCLA, University of Central Florida, University of Pittsburgh, University of Washington (A Cole and collaborators, including R Lehrer and A Waring; P Gupta, L Rohan; D Patton)	
SJ-3991	Multiple mechanisms	ImQuest, IPM	

DISCOVERY/EARLY PRECLINICAL[±]

Candidate	*Mechanism of Action*	*Developer/Researcher/Sponsor*	*Additional Information*
BASANT		A Singh for GP Talwar	*Against Chlamydia trachomatis*
C5A	Vaginal defense enhancer	NIH, Scripps Research Institute, Viriome (F Chisari, P Gallay)	*Mechanism ruptures the integrity of both the viral membrane and the mature core. Currently testing C5A in the HIV vaginal transmission mice model. Plans to test in the HIV vaginal transmission macaque model.*
CADA (Cyclotriazadisul fonamides)	Entry/fusion inhibitor, Uncharacterized mechanism(s)	Rega Institute, University of Nevada, EMPRO (D Schols, TW Bell)	*First and only chemical compound described to down-modulate specifically the human cellular CD4 receptor*
CAP and combinations with NNRTIs and ZFIs	Combination	NIH	
Combinations	Entry inhibitors, Replication inhibitors	IPM	CCR5 blockers
Diterpene	Combination	FAP, FIOCRUZ, UFF (Cirne-Santos C, Castello-Branco L, de Palmer Paixao Frugulhetti I, Teixeira V)	*Dolabelladienetriol blocks the integration of HIV-1 provirus and ablates HIV-1 replication in PBMCs. Noncompetitive inhibitor of reverse transcriptase: additive effect with AZT; synergistic effect with Atazanavir.*
DS003/BMS-599793	Entry/fusion inhibitor	IPM	*gp120 binder*
DS004/L-860,872	Entry/fusion inhibitor	IPM	*CCR5 blocker, will only be developed as combination microbicide with compounds with other mechanisms of action*
DS005/L-860,882	Entry/fusion inhibitor	IPM	*CCR5 blocker, will only be developed as combination microbicide with compounds with other mechanisms of action*
EBd peptides	Entry/fusion inhibitor	NIH, University of Wisconsin School of Medicine	*Funding in process to begin preclinical research*
Flavonoids (EGCG)	Entry/fusion inhibitor	NIAID, NY State Institute for Basic Research, University of Pittsburgh (S Hillier, C Isaacs)	*EGCG: Epigallocatechin Gallate*
Glycerol monolaurate (GML)	Uncharacterized mechanism(s)	NIAID, University of Minnesota (A Haase and P Schlievert)	
HHA, KRV2110, T20 Combinations	Combination	ANRS- Multi Micro Project (Belec L, Jenabian MA, Saidi H, Vanham G)	*In vitro synergistic activities of drug combinations: HHV+KRV2110, HHA+T20, KRV2110+T20)*
ISIS 5320	Entry/fusion inhibitor	ImQuest	
K5-N, OS(H), K50SH	Entry/fusion inhibitor	San Raffaele Scientific Institute and Glycores 2000, EMPRO	*Completing toxicity studies in cervical explants and macrophages – manuscripts being compiled*
KP1, KP17	Replication inhibitor, Combination	CONRAD (K Parang, GF Doncel, HK Agarwal)	
L'644 peptide	Entry/fusion inhibitor	IPM	*gp41 inhibitor*
Maraviroc	Entry/fusion inhibitor	IPM	*CCR5 blocker*
MIV-150 Vaginal Ring	Entry/fusion inhibitor	Population Council	*Preclinical testing of MIV-150 (NNRTI) in a vaginal ring*
Nanobodies™	Entry/fusion inhibitor	University College London, University of Utrecht, Ablynx NV, EMPRO	*Nanobodies/Llama VHH*
NCp7 Thioesters (SAMTs)	Replication inhibitor	ImQuest	

Novasomes	Combination, Entry/fusion inhibitor, Uncharacterized mechanism(s)	Novavax (A DeVico)	
Optimised dendrimers	Combination, Entry/fusion inhibitor	NIH (DAIDS), Reprotect, Starpharma Pty Ltd (J Paull)	*Combination of technology of VivaGel™ containing a dendrimer as the active ingredient (entry/fusion inhibitor) and BufferGel™-related formulation in a combination product*
PC-710	Combination	Population Council	*Carraguard (entry/fusion inhibitor) and Zinc – appears highly effective against HSV-2*
PSC-RANTES	Entry/fusion inhibitor	La Jolla Foundation for Microbicide Research, Mintaka Foundation, NIAID, NIH, Scripps Research Institute, University of Geneva (M Lederman, D Mosier, R Offord, O Hartley and collaborators)	*CCR5 inhibitor*
Pyrimidindiones	Multiple mechanisms	ImQuest	*Funding through SBIR*
Pyrimidindiones and ISIS 5320	Combination (2 products)	ImQuest	*Funding through the MIP*
RANTES peptides	Entry inhibitor	San Raffaele Scientific Institute, Osel, Inc. (Vangelista L, Secchi M, Liu X, Xu Q, Lusso P)	*Development of a live microbicide based on lactobacilli-producing RANTES derivatives.*
Recombinant lactobacillus (LAB)	Entry/fusion inhibitor	Aaron Diamond AIDS Research Center, NIH (D Boden)	*Live microbial anti-HIV microbicide*
REP 9C, REP 9AC	Entry inhibitor	REPLICor Inc., NIH/NIAID (Vaillant A and collaborators)	*Amphipathic DNA polymers attach to viral glycoproteins and neutralize their entry activity, preventing viral infection. This technology has been shown to be well tolerated in rodent, avian and non-human primates species and has demonstrated potent, well tolerated in vivo antiviral activity in representative viruses from seven different viral families including HCV, HBV (DHBV), influenza, respiratory syncytial virus, Herpes simplex-2, cytomegalovirus and Ebola virus.*
sCD4-17b	Entry/fusion inhibitor	NIH (E Berger)	
Single-chain ICAM	Entry inhibitor	Osel, Inc.	*Inhibits cell-associated viral entry*
siRNA	Combination, Entry/fusion inhibitor	Immune Disease Institute, Harvard Medical School, NIH, IPM (J Lieberman)	*siRNA-based microbicide*

Sodium Rutin Sulfate (SRS)	Entry/fusion inhibitor	Zhejiang CONBA Pharmaceutics Company	
Soluble DC-SIGN	Entry/fusion inhibitor	Scripps Research Institute	
Syndecan	Combination	Scripps Research Institute (P Gallay)	*Compounds that neutralize either the mucosal syndecans or the syndecan-binding of HIV-1, gp120; compounds that block gp120-syndecan interactions also block gp120-CCR5 interactions. Shows protective effect against HSV and* N. Gonorrhoeae
Talactoferrin	Entry/fusion inhibitor, Uncharacterized mechanism	Aggenix, Inc. (Cho D, McGowan I, Anton P)	*Preliminary research on human recombinant lactoferrin (talactoferrin) is focused on investigating the in vitro efficacy of this naturally occurring glycoprotein against HIV target cells. Studies suggest inhibition of binding of HIV to target receptors. Low potential for toxicity and adverse effects.*
TATC-D peptides	Entry/fusion inhibitor	NIH, University of Wisconsin School of Medicine	*Funding in process to begin preclinical research*
Unipron	Vaginal defense enhancer	Institute of Primate Research – Dept Reproductive Health (PG Mwethera)	*Formulated, developed and patented in collaboration with Universal Pharmaceutical Cooperation Ltd, which is currently manufacturing Unipron for preclinical/clinical trials. Vaginal lubricant.*
x-REPLAB	Vaginal defense enhancer, Combination	Makerere College of Health Sciences, Restrizymes Canada Corporation, Restrizymes Biotherapeutics LTD (W Misaki, B Wilson, K Henry)	*Modifies native vaginal lactobacilli strains to enhance antimicrobial properties. Combination properties expressed through a 'search and destroy strategy.'*
ZCM (PC-1005)	Combination	Population Council	*Carraguard (entry/fusion inhibitor), Zinc and MIV-150*
Zinc tetra-ascorbo-camphorate derivative "C14"	Combination	MGB Pharma (Belec L, Jenabian MA, Saidi H, Gombert B, Mannarini A)	*Possible entry and pre-integration inhibitor.*

For modifications, please contact Stephanie Tillman, email stillman@microbicide.org.

This table should be considered a draft summary of preclinical candidates, and not a vetted list of viable products. The Alliance is convening a small scientific review panel to discuss this list.

[*]*This list of preclinical microbicide candidates includes those reported by Mapping Exercise respondents, those in published literature and/or recent conference abstracts, and subsequently confirmed by the Researcher/Developer. Many other products exist in preclinical development, without verification by personal correspondence.*

[†]*'Advanced Preclinical' indicates the candidate's success in discovery and initial tests, and likelihood that the product will advance to human trials.*

[+]*All products with plans to file an Investigational New Drug (IND) number application by the fall of 2009 are so indicated by "IND" in the 'Additional Information' column.*

[±]*'Discovery/Early Preclinical' indicates that the candidate is in the very early stages of discovery and testing.*