



ALLIANCE FOR MICROBICIDE DEVELOPMENT

15 February 2008, Volume 9, Number 7

The Alliance for Microbicide Development *News Digest* is an **unedited** compilation of:

- Media coverage of microbicides;
- Abstracts of articles on microbicides and relevant science in peer-reviewed journals;
- Material on other reproductive health and HIV prevention technologies, including HIV vaccines; and
- Matters of policy and politics with importance for microbicide research, development, and advocacy.

Its purpose is to:

- Raise awareness around the range of opinions and information about microbicides disseminated in the press and scientific journals; and
- Provide a neutral, objective basis for decision-making and evidence-based advocacy.

The *News Digest* is produced in a web-based format. Readers can view complete issues of the Digest or search by keyword for individual articles at <http://www.microbicide.org/publications/>. If you would like to be removed from the *Digest* distribution list, please send an email to digest@microbicide.org. We welcome comments, questions, and ideas about other microbicide-relevant topics we might cover, services we might provide, and better ways of providing them!

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1. ALLIANCE UPDATES AND COMMUNITY NEWS

Microbicides Development Programme (MDP) update: MDP301 Phase III trial continues but one arm closes

<http://www.mdp.mrc.ac.uk/>

An independent monitoring committee overseeing the trial of a **vaginal gel** aimed at reducing the spread of HIV has recommended the continuation of the trial but the closure of one arm.

The **Microbicides** Development Programme (MDP) is an international partnership to develop vaginal **microbicides** for the prevention of HIV transmission. The MDP301 trial is studying the candidate **microbicide** PRO 2000/5. There are three arms to the MDP301 trial: women receive a standard prevention package plus one of three gels: 2% PRO 2000/5; 0.5% PRO 2000/5; or placebo gel.

The Independent Data Monitoring Committee (IDMC) for the **Microbicides** Development Programme (MDP) met on 8th February 2008 to examine the data on safety and efficacy collected to date on the MDP301 trial of the candidate **microbicide** PRO 2000/5.

The IDMC recommended that the 0.5% PRO 2000/5 and placebo gel arms should continue. However, as there is no more than a small chance of showing protection against HIV infection from 2% PRO 2000/5 compared to placebo gel, they recommended no further gel should be prescribed to women allocated to the 2% PRO 2000/5 arm of the trial.

The MDP Trial Steering Committee (TSC) met on 11th February 2008 and accepted the recommendations of the IDMC. They noted that the reason for discontinuing the 2% PRO 2000/5 gel arm was because it was unlikely to show benefit rather than because of harm. The TSC considered that it was important to continue recruitment to the 0.5% PRO 2000/5 and placebo arms, as it is still possible that 0.5% PRO 2000/5 will prove to be effective in protecting women against HIV infection.

All women in the 0.5% PRO 2000/5 and placebo gel arms will be asked to continue to use their gel and attend the clinic according to their planned schedule. Recruitment of new participants to the 0.5% and placebo arms will continue.

Women in the 2% PRO 2000/5 gel arm are being contacted and asked to return to their study site as soon as practically possible, bringing with them any unused 2% PRO 2000/5 gel supplies. They will be invited to attend the clinic every three months until they have completed their week 52 visit.

The IDMC will continue to monitor the trial carefully until its planned completion in late 2009.

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2. MEDIA COVERAGE OF MICROBICIDES

"Calif. firm buys Quakertown contraceptive developer"

Date: 13 February 2008

Source: *The Philadelphia Inquirer*

Author(s): Linda Loyd

http://www.philly.com/philly/business/homepage/20080213_Calif__firm_buys_Quakertown_contraceptive_developer.html

Cellegy Pharmaceuticals Inc. said it has agreed to be acquired by Adamis Pharmaceuticals Corp. of San Diego.

Cellegy, of Quakertown, has sought a merger since selling most of its assets in 2006 for \$9 million to ProStrakan Group P.L.C. of Scotland. Cellegy has one potential product, a **microbicide** gel, Savvy, that is in Phase 3 clinical studies in the U.S. as a contraceptive. Earlier Savvy studies for preventing HIV infection were stopped because of lack of evidence that the gel worked.

Detailed financial terms of the merger, which was announced late yesterday and which allows privately-held Adamis to become a publicly-traded company, were not disclosed.

Adamis chief executive officer Dennis Carlo will head the combined company, which will focus on developing products for viral infections, including influenza.

Under the deal, Cellegy will implement a reverse stock split, before the closing, estimated to be between 8.5 to 1 and 9.9 to 1. After the closing, each outstanding share of Adamis common stock will be converted into the right to receive one post-reverse stock split share of Cellegy common stock. Cellegy has about 29.8 million outstanding shares; Adamis has about 50 million outstanding shares.

In 2004, Cellegy bought Biosyn Inc. of Huntingdon Valley and in 2005 moved its corporate headquarters to Pennsylvania from Brisbane, Calif.

Cellegy shares were up 1 cent, or 12.5 percent, to 9 cents in over-the-counter trading.

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3. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

"CD4 mimetic miniproteins: potent anti-HIV compounds with promising activity as microbicides"

Author(s): Van Herrewege Y, Morellato L, Descours A, et al

Reference: N/A Epub ahead of print.

<http://jac.oxfordjournals.org/cgi/content/abstract/dkn042v1?maxtoshow=&HITS=3&hits=3&RESULTFORMAT=&andorexacttitle=and&andorexacttitleabs=and&fulltext=microbicide%2C+microbicides&andorexactfulltext=or&searchid=1&usestrictdates=yes&resourcetype=HWCIT&ct>

Published Abstract: Objectives: The antiviral activity of CD4 miniproteins was evaluated as potential HIV **microbicides**, using relevant in vitro models. Methods: Compounds were tested in a single-cycle HIV-1 pseudovirus assay and against replication competent HIV-1 in co-cultures of monocyte-derived dendritic cells (MO-DC) and CD4+ T cells. Cytotoxic activity was evaluated in an MTT assay. Results: Monomeric miniproteins (M47 and M48) showed

50% effective concentration (EC50) values of 79-105 nM against a subtype B, CCR5 co-receptor-using Ba-L pseudovirus. Higher activity was found for the dimeric miniproteins M48D30, M48D50 and M48D100 (EC50 between 15 and 30 nM), in contrast to the tetrameric miniproteins M48T30, M48T50 and M48T100 (EC50 between 107 and 377 nM). The hetero-bivalent miniprotein M48-Hep and miniproteins that targeted the Phe-43 cavity on gp120 (M48-U1, M48-U2 and M48-U3) were highly active, with EC50 values as low as 2 nM for M48-U1. All miniproteins showed high activity against CCR5 or CXCR4 co-receptor-using subtype B and CRF-01_A/E pseudoviruses. Many early M48-based compounds were much less active against subtype C pseudoviruses, whereas M48-U compounds that targeted the Phe-43 cavity were very active against all pseudoviruses, including subtype C. In MO-DC/CD4+ T cell co-cultures with replication-competent HIV-1 Ba-L, EC50 values ranged between 13 and 1719 nM depending on the miniprotein, with M48-U1, M48-U2 and M48-U3 again being the most potent. Importantly, the latter compounds completely prevented viral replication by treating the cultures from 2 h before until 24 h after infection, at non-toxic concentrations of 66-6564 nM. Conclusions: These novel CD4 miniproteins might constitute a promising class of HIV **microbicides**.

"Microbicides for multidrug-resistant and multitropic HIV-1"

Author(s): D\Cruz OJ, Uckun FM

Reference: N/A 9(2):152-69.

<http://highwire.stanford.edu/cgi/medline/pmid;18246518>

Published Abstract: The most common mode of acquiring HIV-1 is via sexual transmission across the genital mucosa. Topical **microbicides** are a promising prevention strategy for the protection against HIV infection and may ultimately have an impact on the global AIDS pandemic. The effectiveness of a **microbicide** to prevent HIV-1 transmission will depend on the evolutionary and genital transmission dynamics of the viral subtypes, and sexual behavioral characteristics. Contemporary antiretroviral therapy has led to virological failure as a result of HIV-1 reverse transcriptase gene mutations. The transmission of these multidrug-resistant HIV-1 variants, and the superinfection with the same or distinct HIV-1 subtypes and recombination is a formidable hindrance inherent to global **microbicide** development. Consequently, mechanism-based **microbicides** targeting both the cell-free and cell-associated HIV-1 variants and subtypes can be expected to have superior clinical efficacy and safety profiles compared with polymeric anionic **microbicides**. This review describes the discovery of potent anti-HIV-1 agents against multidrug-resistant and multitropic HIV-1 variants with implications for global **microbicide** development. Stampidine and thiourea non-nucleoside reverse transcriptase inhibitors (NNRTIs) have demonstrated highly potent activity against clinically relevant multidrug-resistant and recombinant HIV-1 isolates spanning different subtypes across several continents. Extensive preclinical studies have shown that stampidine and a candidate thiourea NNRTI (HI-443) have clinical potential as a safe combination **microbicide** to inhibit, prevent or treat mucosal HIV-1 infections.

"Pathogenesis of HIV disease: opportunities for new prevention interventions"

Author(s): Fauci AS

Reference: N/A 45(Suppl4):S206-12.

<http://highwire.stanford.edu/cgi/medline/pmid;18190288>

Published Abstract: Current efforts to prevent human immunodeficiency virus (HIV) disease, which largely focus on altering human behavior, have had some notable successes yet have failed to halt the spread of the acquired immunodeficiency syndrome pandemic. A greater understanding of the pathogenesis of HIV disease is providing us with the scientific rationale for additional approaches to prevention. Some of the approaches discussed in this article are available now. For example, we have the means to screen for and treat other sexually transmitted diseases that increase vulnerability to HIV, adult male circumcision is readily available in most properly equipped hospitals, and antiretroviral agents that decrease the viral load help prevent transmission from pregnant women to their infants. Other approaches discussed are under investigation. For instance, numerous topical **microbicides** are in various stages of development, incremental progress is being made toward creation of an HIV vaccine designed to prevent HIV transmission or slow the course of disease in people who become infected, and studies are under way to evaluate the risks and benefits of prophylactic antiretroviral therapy in individuals at high risk for HIV disease.

"Perceptions of anal sex in rural South Africa"

Author(s): Ndinda C, Chimbwete C, McGrath N, et al

Reference: N/A 10(2):205-12.

<http://highwire.stanford.edu/cgi/medline/pmid;18247212>

Published Abstract: As part of the **Microbicides** Development Programme, we conducted formative research to explore perceptions of anal sex at a site in rural KwaZulu-Natal. We were interested in the practice of anal sex because of its potential role in HIV transmission. Eleven focus group discussions were conducted with men and women from rural areas and in a semi-urban township. Participants were asked about their knowledge of and attitudes towards anal sex, and its practice in the local population. Findings indicate that in discussion anal sex was confused with other non-traditional sexual practices like vaginal sex 'dog-style' and with oral sex. Discussion of anal sex among those who had heard about it linked it to socially marginal groups and asymmetrical power relations.

"The effects of spermicides containing nonoxynol-9 on cervical cytology"

Author(s): Halpern V, Rountree W, Raymond EG, et al

Reference: N/A 77(3):191-94.

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T5P-4RPVJ63-8&_user=10&_coverDate=03%2F31%2F2008&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C00050221&_version=1&_urlVersion=0&_userid=10&md5=e0096f3bd2c65de66f5b154f035abc8d

Published Abstract: *Background* This analysis was undertaken to compare the effect of the different dosages and formulations of spermicides containing nonoxynol-9 (N-9) on cervical cytology. *Study Design* A randomized trial was conducted at 14 sites in the United States to evaluate the effectiveness and safety of five spermicides containing N-9. This Papanicolaou smear analysis included the data from all participants who provided two Papanicolaou smear samples: at admission and after discontinuation of the product. The effects of the spermicides were evaluated by comparing the rates of alteration of cervical cytology between five study groups. *Results* A total of 640 women were included in this analysis. The majority of the study participants (greater than 85%) had no change of their baseline Papanicolaou smear result. The rates of alteration of cervical cytology were similar among women using the three gels containing the different doses of N-9 and three different formulations containing the same dose of N-9. Our analysis found no association between alteration of cervical cytology and duration or frequency of use of the five study spermicides. *Conclusions* Exposure to different formulations and doses of spermicides containing N-9 is unlikely to influence cervical cytology.

"Vaginal distribution of Replens(R) and K-Y(R) Jelly using three imaging techniques"

Author(s): Mauck CK, Katz D, Sandefer EP, et al

Reference: N/A 77(3):195-204.

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T5P-4RPVJ63-7&_user=10&_coverDate=03%2F31%2F2008&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C00050221&_version=1&_urlVersion=0&_userid=10&md5=043e8f5375a67ab2ed1570db92e82a76

Published Abstract: *Background* Determination of vaginal distribution is important to the development of potential vaginal **microbicial** or spermicidal products. *Study Design* This was a descriptive study of three imaging techniques with a randomized crossover assignment of two gels and activity status within each technique. *Method* Each of three sites utilized one technique. Three nulligravid women and three parous women were to be enrolled at each site. We studied the effects of time, ambulation, parity and body mass index on vaginal spreading of two commonly used gels, K-Y(R) Jelly and Replens(R). Imaging by magnetic resonance imaging and gamma scintigraphy was performed at 5, 20, 35 and 50 min after insertion of 3.5 mL of gel. Imaging with a fiberoptic probe was performed at 5 and 20 min after insertion. *Results* Initial application of the gel resulted in approximately two thirds of maximum coverage possible, both in linear extent along the vaginal axis and in surface area covered. Over the next 45 min, spreading increased to about three quarters of the maximum possible. Ambulation generally increased linear spreading and the proportions of women with gel at the introitus and os. Effects of parity and body mass index (BMI) were similar on most measures of gel spreading, with nulligravid women tending toward greater spread than parous women and women of high BMI usually showing somewhat greater spread than women of normal weight. Differences between the two gels were not seen when all conditions of application were considered together. *Conclusion* In vivo imaging of gel distribution demonstrated that ambulation, parity and BMI affect **vaginal gel** spreading. The three imaging techniques have

advantages and disadvantages and provide complementary information for **microbicide** development.

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4. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

"Defining, designing, implementing, and evaluating Phase 4 HIV prevention effectiveness trials for vulnerable populations"

Author(s): Kelly JA, Spielberg F, McAuliffe TL, et al

Reference: N/A 47(Supplement):S28-33.

<http://www.jaids.org/pt/re/jaids/abstract.00126334-200803011-00006.htm;jsessionid=HxpQkP0Z9ndF4vmpRcS3p24gngK42k2tLJvhFnhDBh1QkbZzfvTn!-1108188142!181195628!8091!-1>

Published Abstract: Summary: The efficacy of behavioral HIV prevention interventions has been convincingly demonstrated in a large number of randomized controlled phase 3 research outcome trials. Little research attention has been directed toward studying the effectiveness of the same interventions when delivered by providers to their own clients or community members, however. This article argues for the need to conduct phase 4 effectiveness trials of HIV prevention interventions that have been found efficacious in the research arena. Such trials can provide important information concerning the impact of interventions when applied in heterogeneous "real-world" circumstances. This article raises design issues and methodologic questions that need to be addressed in the conduct of phase 4 trials of behavioral interventions. These issues include the selection and training of service providers engaged in such trials, maintenance of fidelity to intervention protocol in provider-delivered interventions, determination of intervention core elements versus aspects that require tailoring, selection of relevant phase 4 study outcomes, interpretation of findings indicative of field effectiveness, sustainability, and other aspects of phase 4 trial design.

"Feline immunodeficiency virus dendritic cell infection and transfer"

Author(s): Sprague WS, Robbiani M, Avery PR, et al

Reference: N/A 89(Pt 3):709-15.

<http://vir.sgmjournals.org/cgi/content/abstract/89/3/709?maxtoshow=&HITS=1&hits=1&RESULTFORMAT=&andorexacttitle=and&andorexacttitleabs=and&fulltext=microbicide%2C+microbicides&andorexactfulltext=or&searchid=1&usestrictdates=yes&resourcetype=HWCIT&ct>

Published Abstract: Feline immunodeficiency virus (FIV) interacts with dendritic cells (DC) during initiation of infection, but whether DC support or transfer FIV infection remains unclear. To address this issue, we studied the susceptibility of feline myeloid DC to FIV infection and assessed potential transfer of infection from DC to CD4+ T

cells. FIV was detected in membrane-bound vesicles of DC within 2 h of inoculation, although only low concentrations of FIV DNA were found in virus-exposed isolated DC. Addition of resting CD4+ T cells increased viral DNA levels; however, addition of activated CD4+ T cells resulted in a burst of viral replication manifested by FIV p27 capsid antigen generation. To determine whether transfer of FIV infection required productively infected DC (vs virus bound to DC but not internalized), virus-exposed DC were cultured for 2 days to allow for degradation of uninternalized virus and initiation of infection in the DC, then CD4+ T blasts were added. Infection of T cells remained robust, indicating that T-cell infection is likely to be mediated by de novo viral infection of DC followed by viral transfer during normal DC/T-cell interactions. We conclude that feline DC support restricted FIV infection, which nevertheless is sufficient to efficiently transfer infection to susceptible T cells and trigger the major burst of viral replication. Feline DC/FIV/T-cell interactions (similar to those believed to occur in human immunodeficiency virus and simian immunodeficiency virus infections) highlight the means by which immunodeficiency-inducing lentiviruses exploit normal DC/T-cell interactions to transfer and amplify virus infection.

"HIV-1 envelope protein binds to and signals through integrin 47, the gut mucosal homing receptor for peripheral T cells"

Author(s): Arthos J, Cicala C, Martinelli E, et al

Reference: N/A Epub ahead of print.

<http://www.nature.com/nature/journal/vaop/ncurrent/abs/ni1566.html>

Published Abstract: Infection with human immunodeficiency virus 1 (HIV-1) results in the dissemination of virus to gut-associated lymphoid tissue. Subsequently, HIV-1 mediates massive depletion of gut CD4+ T cells, which contributes to HIV-1-induced immune dysfunction. The migration of lymphocytes to gut-associated lymphoid tissue is mediated by integrin 47. We demonstrate here that the HIV-1 envelope protein gp120 bound to an activated form of 47. This interaction was mediated by a tripeptide in the V2 loop of gp120, a peptide motif that mimics structures presented by the natural ligands of 47. On CD4+ T cells, engagement of 47 by gp120 resulted in rapid activation of LFA-1, the central integrin involved in the establishment of virological synapses, which facilitate efficient cell-to-cell spreading of HIV-1.

EDITOR'S NOTE: A media write-up of this article is available for public access at

http://news.yahoo.com/s/nm/20080210/hl_nm/aids_infection_dc

"Mathematical models for HIV transmission dynamics: tools for social and behavioral science research"

Author(s): Cassels S, Clark SJ, Morris M

Reference: N/A 47(Supplement):34-39.

<http://www.jaids.org/pt/re/jaids/abstract.00126334-200803011-00007.htm;jsessionid=HxpPvBYh92GcfXIYxyHcLNhmfPThfVByvznll128fzPYqTfHvblb!->

809317659!181195629!8091!-1

Published Abstract: Summary: HIV researchers have long appreciated the need to understand the social and behavioral determinants of HIV-related risk behavior, but the cumulative impact of individual behaviors on population-level HIV outcomes can be subtle and counterintuitive, and the methods for studying this are rarely part of a traditional social science or epidemiology training program. Mathematical models provide a way to examine the potential effects of the proximate biologic and behavioral determinants of HIV transmission dynamics, alone and in combination. The purpose of this article is to show how mathematical modeling studies have contributed to our understanding of the dynamics and disparities in the global spread of HIV. Our aims are to demonstrate the value that these analytic tools have for social and behavioral sciences in HIV prevention research, to identify gaps in the current literature, and to suggest directions for future research.

"Mentoring the next generation of HIV prevention researchers: a model mentoring program at the University of California San Francisco and Gladstone Institute of Immunology and Virology Center for AIDS Research"

Author(s): Kahn J, Des Jarlais CD, Dobkin L, et al

Reference: N/A 47(Supplement):S5-S9.

<http://www.jaids.org/pt/re/jaids/abstract.00126334-200803011-00002.htm;jsessionid=HxyXX7hnh2xpCCmpnCPNJ40INHlYpvk5cPlp2TvdkBGQv1RrtWtg!-1108188142!181195628!8091!-1>

Published Abstract: Purpose: Mentoring is critical to develop and nurture early career investigators, helping them to succeed in building networks of colleagues, and is especially important for investigators focused on HIV research. We piloted a multidiscipline mentoring program targeting postdoctoral scholars and early career faculty concentrating on HIV/AIDS research. Method: The pilot mentoring program was conducted at the Center for AIDS Research (CFAR) at the University of California San Francisco and the Gladstone Institute of Virology and Immunology. Mentees were self-referred postdoctoral scholars and early career faculty. Mentors were drawn from the senior faculty. Early career mentees were matched with senior investigators for individual meetings, a monthly workshop on topics directed by the mentees, and single-day mentoring seminars. Results: More than 30 mentees and 20 mentors have participated in the pilot project. Most mentees reported that the 1-on-1 mentoring was a satisfying experience. The most highly valued activities were those that facilitated networking among mentees, networking between mentors and mentees, and workshops that focused on grant applications and first academic appointments and promotions. Conclusions: A multidisciplinary mentoring program for postdoctoral scholars and early career faculty focused on HIV/AIDS research is valuable. Umbrella organizations, such as the CFAR, are well suited to create and provide highly valued mentoring experiences.

"Probing the structural states of human immunodeficiency virus type 1 Pr55gag by using monoclonal antibodies"

Author(s): LeBlanc JJ, Perez O, Hope TJ

Reference: N/A 82(5):2570-74.

<http://jvi.asm.org/cgi/content/abstract/82/5/2570?etoc>

Published Abstract: Gag-FP (fluorescent protein) fusion constructs are commonly used to study human immunodeficiency virus type 1 assembly, yielding diffuse signals throughout the cytoplasm along with punctate signals routinely described as virus-like particles (VLPs) representing assembled but unprocessed Gag. However, these particles cannot be accurately described as VLPs, since fluorescence microscopy cannot provide structural resolution. We demonstrate here that the inability of a monoclonal p24 antibody to bind its cognate epitope when unprocessed Gag is assembled distinguishes VLPs from unassembled, monomeric Gag. Furthermore, we show that assembled and unassembled Gag punctate signals travel along microtubules. These monoclonal antibody studies provide a new tool for examining retroviral assembly.

"Proposal for the development of a standardized protocol for assessing the economic costs of HIV prevention interventions"

Author(s): Pinkerton SD, Pearson CR, Eachus SR, et al

Reference: N/A 47(Supplement):S10-S14.

<http://www.jaids.org/pt/re/jaids/abstract.00126334-200803011-00003.htm;jsessionid=HxpJfCpChnvdFNX9G8CbpC7YZPtwhTwrX4F1FsBV7YmhISLYrVkl-1108188142!181195628!8091!-1>

Published Abstract: Summary: Maximizing our economic investment in HIV prevention requires balancing the costs of candidate interventions against their effects and selecting the most cost-effective interventions for implementation. However, many HIV prevention intervention trials do not collect cost information, and those that do use a variety of cost data collection methods and analysis techniques. Standardized cost data collection procedures, instrumentation, and analysis techniques are needed to facilitate the task of assessing intervention costs and to ensure comparability across intervention trials. This article describes the basic elements of a standardized cost data collection and analysis protocol and outlines a computer-based approach to implementing this protocol. Ultimately, the development of such a protocol would require contributions and "buy-in" from a diverse range of stakeholders, including HIV prevention researchers, cost-effectiveness analysts, community collaborators, public health decision makers, and funding agencies.

"Rational design of novel HIV-1 entry inhibitors by RANTES engineering"

Author(s): Vagelista L, Secchi M, Lusso P

Reference: N/A Epub ahead of print.

<http://www.ncbi.nlm.nih.gov/pubmed/18243436>

Published Abstract: The discovery that the CC chemokines RANTES, MIP-1alpha and MIP-1beta act as potent natural inhibitors of HIV-1, the causative agent of AIDS, and the subsequent identification of CCR5 as a major virus coreceptor have triggered a wealth of basic and applied research approaches aimed at developing safe and effective viral entry inhibitors. Some of these efforts have focused on RANTES engineering with the goal of enhancing the antiviral activity of the native molecule while reducing or abrogating its inflammatory properties. The wavefront generated a decade ago is still on its course, with a flow of promising leads constantly emerging and being evaluated in preclinical studies. Here, we present an overview of this rapidly evolving field, highlighting the most important features of RANTES molecular architecture and structure-function relationships.

"The ADAPT-ITT Model: a novel method of adapting evidence-based HIV interventions"

Author(s): Wingood GM, DiClemente RJ

Reference: N/A 47(Supplement):S40-S46.

<http://www.jaids.org/pt/re/jaids/abstract.00126334-200803011-00008.htm;jsessionid=HxpKJLWW1kgVtYcr554HsGxQBmRkF98s73L7yndvKT4G57wdKkqL!-1108188142!181195628!8091!-1>

Published Abstract: Summary: The Institute of Medicine (IOM) recommends the use of HIV prevention interventions with proven efficacy to avert new infections. Given the time and cost associated with the development, implementation and evaluation of efficacious HIV interventions, adapting existing evidence-based interventions (EBIs) to be appropriate for a myriad of at-risk populations may facilitate the efficient development of new EBIs. Unfortunately, few models of theoretic frameworks exist to guide the adaptation of EBIs. Over the past few years, the authors have systematically developed a framework for adapting HIV-related EBIs, known as the "ADAPT-ITT" model. The ADAPT-ITT model consists of 8 sequential phases that inform HIV prevention providers and researchers of a prescriptive method for adapting EBIs. The current article summarizes key components of the ADAPT-ITT model and illustrates the use of the model in several case studies.

"Two amino acid substitutions within first external loop of CCR5 induce HIV blocking antibodies in mice and chicken"

Author(s): Pastori C, Clivio A, Diomedede L, et al

Reference: N/A Epub ahead of print.

<http://highwire.stanford.edu/cgi/medline/pmid;18256149>

Published Abstract: Antibodies to the first loop (ECL1) of CCR5 have been identified in HIV-exposed uninfected individuals (ESN) and in HIV-positive non-progressing subjects. Thus, these antibodies may confer resistance against HIV infection. To define which amino acids involved in antibody binding to CCR5, we performed a peptide scanning assay and we studied the immunogenicity of peptides in animal models. A panel of synthetic peptides spanning the CCR5-ECL1 region, displaying Glycine or Alanine substitutions, was assayed for antibody binding with a pool of natural anti-CCR5 antibodies. We used mouse and chicken to study the immunogenicity of mutagenized peptide. Structural characterization by NMR spectroscopy and molecular dynamics simulations were performed to better understand the structural and conformational features of the mutagenized peptide. Amino acid substitutions in positions Ala95 and Ala96 (A95-A96) increased antibody-peptide binding in comparison with wild-type peptide (Phe95-Asp96). Ala95-96 peptide was shown to induce, in mice and chicken, antibodies displaying biological activity at very low concentrations. Strikingly, chicken antibodies to Ala95-96 specifically recognize human CCR5 molecules, downregulate receptor from lymphocytes, inhibit CCR5-dependent chemotaxis and prevent infection of several R5-viruses, displaying IC50 to less than 3 ng/ml. NMR spectroscopy and molecular dynamics simulations proved the high flexibility of isolated epitopes and suggested that Ala95-96 substitutions determine a slightly higher tendency to generate helical conformations combined with a lower steric hindrance of the side chains in the peptides. These findings may be relevant to induce strong and efficient HIV blocking antibodies.

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5. HIV/AIDS VACCINES

"A vaccine strategy against AIDS: An HIV gp41 peptide immunization prevents NKp44L expression and CD4+ T cell depletion in SHIV-infected macaques"

Author(s): Vieillard V, Le Grand R, Dausset J, et al

Reference: N/A 105(6):2100-104.

<http://www.pnas.org/cgi/content/abstract/105/6/2100?etoc>

Published Abstract: We previously showed that a gp41 peptide (3S) induces expression of a natural killer (NK) ligand (NKp44L) on CD4+ T cells during HIV-1 infection and that those cells are highly sensitive to NK lysis. In HIV-infected patients, anti-3S antibodies are associated with the maintenance of CD4+ T cell counts close to their baseline values, and CD4+ T cells decrease with the antibody titer. This study sought to determine whether anti-3S immunization could prevent NKp44L expression on these CD4+ T cells in vivo and inhibits the subsequent decline in CD4+ T cell counts by immunizing macaques with 3S and then infecting them with simian HIV162P3. The results show that anti-3S antibodies inhibited NKp44L expression and NK activity and cytotoxicity. They also decreased the apoptosis rate of CD4+ T cells in peripheral blood and lymph nodes. These data raise questions about the pathogenesis of HIV and present opportunities for both preventive and therapeutic HIV vaccine strategies.

"Novel vaccination protocol with two live mucosal vectors elicits strong cell-mediated immunity in the vagina and protects against vaginal virus challenge"

Author(s): Li Z, Zhang M, Zhou C, et al

Reference: N/A 180(4):2504-13.

<http://www.ncbi.nlm.nih.gov/pubmed/18250460>

Published Abstract: Most HIV infections result from heterosexual transmission to women. Because cellular immunity plays a key role in the control of the infection, we sought to strengthen cellular immune responses in vaginal tissue. We explored a novel prime-boost protocol that used two live mucosal agents that trigger different pathways of innate immunity and induce strong cellular immunity. Adenovirus serotype 5 (Ad5) has frequently been used as a boost for DNA vaccines. In this study we used attenuated, recombinant L. monocytogenes-gag (rLm-gag) to prime mice by various mucosal routes-oral, intrarectal, and intravaginally (ivag)-followed by a systemic or mucosal boost with replication-defective rAd5-gag. Mice primed with a single administration of rLm-gag by any route and then boosted with rAd5-gag intramuscularly exhibited abundant Gag-specific CD8 T cells in spleen and vaginal lamina propria. Conversely, when boosted with rAd5-gag ivag, the immune response was reoriented toward the vagina with strikingly higher CD8 T cell responses in that tissue, particularly after ivag immunization by both vectors (ivag/ivag). Five weeks to 5 mo later, ivag/ivag-immunized mice continued to show high levels of effector memory CD8 T cells in vagina, while the pool of memory T cells in spleen assumed a progressively more central memory T cell phenotype. The memory mice showed high in vivo CTL activity in vagina, a strong recall response, and robust protection after ivag vaccinia-gag challenge, suggesting that this prime-boost strategy can induce strong cellular immunity, especially in vaginal tissues, and might be able to block the heterosexual transmission of HIV-1 at the vaginal mucosa.

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6. OTHER PREVENTION APPROACHES

"Smart pillbox takes on TB"

Date: 13 February 2008

Source: *in-Pharma Technologist.com*

Author(s): Huw Kidwell

<http://www.in-pharmatechnologist.com/news/ng.asp?n=83211&m=1IPE214&c=ctekxoihhlwjezb>

In the fight against tuberculosis in Africa a group from Massachusetts Institute of Technology has invented a smart electromechanical pill box designed to help patients comply with their treatment.

This device, called the uBox, makes sure that the patient takes his/her full regimen of treatment which is crucial to the success of TB therapy. If a patient misses taking part of the course of treatment then resistant strains of the bacterium can develop and produce more severe forms of the disease in the future.

The uBox was developed by Manish Bhardwaj, who is a doctoral student in the Department of Electrical Engineering and Computer Science (Microsystems Technology Laboratories). He was becoming increasingly concerned about ways to help cure tuberculosis sufferers in Asia and Africa.

"The problem is, how do you get people to take this complex regimen" he asked.

The disease claims two million lives in Africa every year and although modern medicine has the means to cure it using a combination of strong antibiotics the problem arises from the strict regimen of treatment.

In effect the patients cannot be trusted to take the full course of treatment every day over a six month period. The mode of treatment has to be very strict to achieve success.

Manish Bhardwaj added "How do you know if pills are getting to the patients or if patients are taking them? Today, there's no good way of doing this... people fail to take all their pills... it is possible to do harm by treatment that doesn't have good adherence. Even missing a few pills can lead to the development of resistant strains, which can then be spread by that noncompliant patient. The people they infect have no chance."

In order to do this the MIT team developed the uBox which has 14 cells in it to accept the daily dose of treatment (solid dosage forms) for a 14 day period. The box is designed to dispense from one chamber per day and the patient is warned with a flashing light and a buzzer as to when they need to take the cocktail of pills.

The uBox does not allow double dosing, as only one compartment will open per day. The patient then uses the box for two weeks and then a health worker refills the box and can also check on patient compliance at the same time by recording digital data as to the time of usage by inserting a 'key like' device into the uBox.

The health workers will also carry a mobile phone/PDA device, the uPhone, to record patient temperature, weight, and also medical history and symptom-related questions. All of this information is then transferred to the patient's confidential records.

A clinical trial using the new system started in India in January 2008. A team from MIT travelled to Bihar province and trained 22 health workers to use the uBox and uPhone. In March 2008 the trial will start properly using 100 uBoxes and 10 uPhones. If this is successful 1,000 uBoxes will be produced for a second trial.

The project has also garnered the interest of the Bill and Melinda Gates Foundation, who may provide support. The potential for the uBox is unlimited, not just confined to TB - it has equal value for anyone that needs to take daily medication.

"Africa: No sex, please - you're HIV-positive"

Date: 08 February 2008

Source: *Inter Press Service News Agency*

Author(s): Sharon Davis

<http://allafrica.com/stories/200802080955.html>

HIV/AIDS policies and programmes disregard the sexual needs of people living with the virus, claim a number of HIV-positive women who attended the third Africa Conference on Sexual Health and Rights -- held this week in Nigeria.

The initiatives focus on prevention and treatment, they add, ignoring the fact that people living with HIV/AIDS who are conducting normal lives still want to experience sexual pleasure, and have children.

"The epidemic has evolved. HIV-infected people are not dying; we are living and we are having sex," noted Beatrice Were, an activist in Uganda for the Global AIDS Alliance, a non-profit based in Washington.

She said health care providers and others are shocked when they discover that a person living with HIV/AIDS is either interested in or having sex, viewing this as irresponsible -- even though condoms have been shown to be highly effective in preventing transmission of the HI virus, and re-infection of a person who has already tested positive.

"We are looked upon as patients who need to be pitied, patients who must be told what to do -- and this includes to abstain from sex, and not to fall pregnant," added Were, who has been HIV-positive for 16 years. "We are treated with bias, even though we are capable of enjoying sexual pleasure without passing on the disease."

Furthermore, noted Belinda Tima -- board co-chair of the International Community of Women Living with HIV/AIDS (ICW), a charity headquartered in London -- sexual pleasure need not be limited to penetrative sex, but can take a variety of forms.

Even the staunchest advocate of condom use cannot claim that the prophylactics are completely effective, however. Is there perhaps a sense among health workers that even the small risk of someone contracting the virus during protected sex with an HIV-positive person is too great?

"Condoms are not 100 percent safe -- we refer to it as 'safer sex' -- but the risk of infection is minimal," responded Anne Ntombela, the ICW's programme director for South Africa. "If you understand the nature of HIV and how it is transmitted you will know that it is not as easy as people think. It needs exposure for a sufficient period of time under the right conditions, and it needs an exit and entry point," she added, in reference to cuts, sores and the like.

The larger issue at play is a moral one, Ntombela said. "Health care workers try to force their moral values on other people, but in reality people will not stop having sex. They would be better served if they were told how to have safer sex, rather than not to engage in sex at all."

In addition, countries should create "...an environment that supports access to services. We need prevention tools like female condoms...and we need more co-operative research on living with HIV and AIDS, and policies and programmes that take cognisance of this."

Pregnancy prevention

Concerns about the sexual activity of HIV-positive people extend to the matter of pregnancy.

HIV-positive women may pass on the virus to children during pregnancy, labour or while breastfeeding. ARVs can reduce the risk of transmission to under two percent, according to AVERT, a global charity that helps combat the pandemic. However, research has indicated persistent fears about mother-to-child transmission of HIV, and that mothers who are HIV-positive could die -- leaving behind orphans who may receive insufficient care.

"When I chose to have a baby 15 months ago people demanded to know why I took the risk of infecting my child. There was a 98 percent probability of not infecting my baby -- but people...demanded to know why I took that two percent risk," said Rolake Odetoyinbo, executive director of Positive Action for Positive Treatment, a non-governmental group in Nigeria. She has lived with HIV/AIDS for a decade.

A number of delegates at the conference claimed that certain clinics administer contraceptive injections when providing AIDS treatment to women, without receiving the consent of these women or counseling them. There are also reports of health workers acting judgmentally towards HIV-positive women in search of reproductive health care, and even denying them assistance. Indications are that women with the virus may be pressed into having an abortion where this option is available, or into being sterilised.

But even in the face of these difficulties, an array of factors prompt women living with HIV/AIDS to become pregnant or remain so, notes a 2002 report by Ipas, 'Reproductive choice and women living with HIV/AIDS'. Ipas is an international organisation for the advancement of women's sexual and reproductive rights.

It states that "...often younger women appear to be most motivated by a desire for motherhood and the idea that having a child will give them more hope. In a few cases, personal convictions that abortion is wrong may prevent them from seeking terminations, so that they end up having children 'by default'."

Social expectations as concerns family size, the stigma surrounding childlessness and unsuccessful attempts to terminate pregnancy also play a role. In addition, childbearing can be seen as "...a means of obtaining or ensuring economic support from partners".

Noted the ICW's Ntombela, diagnosed with HIV 17 years ago, "All pregnancy is risky. Telling an HIV-infected woman not to have a child is the same as telling all women not to have a child in case it is born with a defect, in case it has Down's syndrome."

"There are worse complications than HIV for a child HIV-infected children can experience a healthy life style -- it's not like 10 years ago."

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EDITOR'S NOTE: The full text of this article is available for public access at the above website.

7. POLITICS AND POLICY

"Kevin De Cock: guiding HIV/AIDS policy at WHO"

Source: *Lancet Infectious Diseases*. 2008 Feb;8(2):98-100.

Author(s): Priya Shetty

<http://www.thelancet.com/journals/laninf/article/PIIS147330990870015X/fulltext>

Kevin De Cock is director of WHO's HIV/AIDS department. Formerly director of the US Centers for Disease Control and Prevention in Kenya, he is an infectious disease specialist, with expertise in HIV/AIDS, tuberculosis, liver disease, and tropical diseases such as yellow fever and viral haemorrhagic fevers.

EDITOR'S NOTE: *The following is an excerpt of a longer interview. A free subscription is required to view the entire interview at the above website.*

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TLID: How important is women's empowerment in fighting the HIV epidemic, especially in Africa?

KDC: Gender equity is extremely important for public health and for social justice. I think one needs to be careful before saying that there are macro-level explanations for the AIDS epidemic and that if we could only change that aspect it would all be fine. Botswana, for example, is a fair country in terms of the role of women and the respect for their rights, but it has one of the worst HIV/AIDS epidemics in the world. Some of the factors fuelling its high rate include rates of sexual partner change, lack of male circumcision, and high frequency of genital herpes. So you need to work on all these levels: behaviour change, biomedical interventions, human rights, and structural change.

However, for women's health in general, the issues of equity, economic empowerment, and human rights are all immensely important. And helping women to gain power over their sexual and reproductive choices is a key strategy to tackling the AIDS epidemic.

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8. HIV/AIDS FUNDING

"Gates Foundation head to leave longtime post"

Date: 07 February 2008

Source: *The New York Times*

Author(s): Stephanie Strom

<http://www.nytimes.com/2008/02/07/us/07charity.html?ref=world>

Patty Stonesifer, who helped start the Bill and Melinda Gates Foundation in an office over a pizza parlor seven years ago and has overseen its growth it into the world's largest philanthropic institution, said in an interview on Wednesday that she would step down by the end of the year. Her decision marks a major turning point for the foundation, which has operated largely as a family foundation overseen by Ms. Stonesifer, a friend and confidante of Bill Gates, a co-founder of Microsoft.

The arrival of a new chief executive, possibly an outsider, is the last step in the foundation's transition to a more orthodox institutional structure, with clearly defined divisions knit together by a central management team that Ms. Stonesifer has assembled over the last two years. The announcement is likely to surprise the world of philanthropy, which has watched the growth of the Gates Foundation with a mixture of awe, fear and envy.

With \$37 billion in assets, it is nearly four times the size of the next largest foundation. It dispenses more than \$3 billion annually, more than five times the amount distributed by the Ford Foundation, and will have some 800 employees by year's end.

"This job is mind-boggling because it requires a wholly different skill set than any other job in the philanthropic world," said Harvey P. Dale, a professor of philanthropy and nonprofit law at New York University. "It's an enormous challenge."

Ms. Stonesifer, 51, who has worked for a dollar a year after earning millions as a senior executive at Microsoft, said she was comfortable stepping down now because she believed the foundation had firmly established strategies for achieving its primary goals of improving health, education and nutrition around the world. "It's the right time," she said. "We have a lot of momentum now, our strategies are in place, and it's time to take the organization to the next level where we deliver on those strategies."

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EDITOR'S NOTE: The full text of this article is available for public access at the above website.

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9. ANNOUNCEMENTS

Spousal Agreement on Family Planning in Sub-Saharan Africa

http://www.measuredhs.com/pubs/pub_details.cfm?id=735

This Demographic and Health Survey Publication, written by Tesfayi Gebreselassie and Vinod Mishra and Macro International Inc., investigates spousal agreement on approval of family planning, spousal agreement on discussion of family planning, and wife's use of a modern contraceptive method. The analysis uses matched couples' data from Demographic and Health Surveys (DHS) conducted between 1999 and 2004 in Benin, Burkina Faso, Chad, and Mali in West and Central Africa, and Malawi, Namibia, Rwanda, Uganda, Zambia, and Zimbabwe in Eastern and Southern

Africa. In addition, pooled data from the 10 countries are used to examine how polygyny, as an institution of marriage rather than an individual characteristic, influences spousal approval of family planning and discussion of family planning.

Upcoming Conferences of Interest

<http://www.microbicide.org/microbicideinfo/reference/ConferenceMatrix15Feb2008.pdf>

The Alliance for **Microbicide** Development actively seeks information on conferences of interest for the **microbicide** field and overall HIV and STI prevention community. A monthly updated table will be available on our website with conference titles, locations, and important dates, including early-bird registration and abstract submission. A reminder of this updated table will appear in the last Digest of every month. Please alert Alliance Communications Manager, Latifa Boyce, of any conferences that might also be included, by email: lboyce@microbicide.org.

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