Cash infusion for HIV microbicides

The flagging microbicide field has been given a shot in the arm with $130 million in grants pledged to the International Partnership for Microbicides (IPM) to advance new formulations. The Bill and Melinda Gates Foundation committed $100 million and the UK Department for International Development (DFID) in London pledged $28.5 million to Maryland-based IPM, a nonprofit product development partnership. The announcement made in February followed encouraging results of a phase 2 trial of PRO2000, a vaginal microbicide produced by 5 Chadds Ford, Pennsylvania-based Endo (formerly Interneuron, then Indevus). The latter study represents a milestone as it is the first to support the concept that a vaginal microbicide can protect women from HIV infection. But the results are not conclusive, and critics question whether the strategy is still worth pursuing, as two decades of development have yielded nothing but disappointment. Optimism now hinges on novel formulations containing antiretroviral compounds, which, IPM contends, offer promise in the near term while the search for an effective HIV vaccine continues.

To date, big pharma has largely ignored topical microbicides in the HIV field, so development efforts have depended on public funding aided by a handful of small biotech companies. In 2008, according to a report by the HIV Vaccine and Microbicides Resources Tracking Working Group, total global investment in R&D in 2007 was $226.5 million—the public sector provided 90% of these funds, the philanthropic sector provided 8% and the commercial sector accounted for only 2%.

Despite the low levels of commercial activity, currently 15 clinical trials are testing 9 different microbicide candidates, and a further 16 trials are planned. A clutch of biotech companies are investing in these initiatives. Albert Profy, vice president of preclinical development at Endo, is the program leader for PRO2000, a polyanionic, lipophilic bisarylsulfonate microbicide that binds to HIV (HIV and other sexually transmitted pathogens, such as herpes simplex virus), interfering with viral attachment and transfer across the epithelium. In early February, the company released results from a National Institutes of Health–sponsored trial of 3,099 women in Africa and the US. The gel appeared to protect 30% better than placebo, but researchers are awaiting results of a UK study on 9,000 women.

The field has been dogged by several prominent HIV microbicide late-stage failures, which have dampened enthusiasm for the field. The first products to be tested were licensed spermicides containing nonoxynol-9 (N-9), a compound with potent anti-HIV activity *in vitro*. But N-9 and other similar surfactants cause genital epithelial disruption and inflammation, and a recent multicenter randomized placebo-controlled trial of a low dose N-9 formulation demonstrated an increased incidence of HIV infection in

Fresh hope in microbicides. Topical vaginal gels containing novel antiretrovirals are being tested against placebo gels, here pictured, to prevent HIV transmission in women.

Table 1 Selected vaginal microbicidal gels in development

Product	Description	Company	Status
PRO 2000 (bis-arylsulfonate)	Polyanionic lipophilic polymer	Indevus/Endo	Phase 3
Viread (tenofovir)	Gel version of nucleotide analog reverse transcriptase inhibitor	Gilead Sciences	Phase 2b
VivaGel (SPL 7013)	A dendrimer with naphthalene disulfonic acid surface groups	Starpharma	Phase 1/2
UC-781 (oxathin carboxanilide)	Gel version of nonnucleoside reverse transcriptase inhibitor	Cellegy Pharma (S. San Francisco, California)	Phase 1

the N-9 group compared to placebo. Two other major microbicide studies were halted in 2007 after Polydex Pharmaceuticals of Toronto, Ontario, reported that women who received UsherCell (cellulose sulfate) were more likely to become infected (*N. Engl. J. Med.* **359**, 463–472, 2008). The latest casualty was New York-based Population Council, which announced last December that its microbicide Carraguard (λ-/κ-carrageenan) had failed to show efficacy in a randomized, double-blind trial of >6,000 South African women (*Lancet* **372**, 1977–1987, 2008).

Endo's Profy agrees that previous lackluster results have discouraged investment in the field, but notes that his company "believed in the product and was willing to take the risk." Indeed, recent results with PRO2000 could signal a 'turning point' for microbicides, he believes. "It is important to note that the study was a phase 2b trial designed to determine whether candidate microbicides showed sufficient promise for testing in a larger phase 3 study," Profy adds. "It was not statistically significant, but it certainly met the criteria specified for continued development."

Elsewhere, Starpharma of Melbourne, Australia, is currently working on VivaGel, a polylysine dendrimer. This topical gel acts by a non-specific mechanism similar to that of PRO2000, blocking pathogen entry into healthy epithelial cells. Jackie Fairley, CEO of Starpharma, believes that past failed trials have provided a useful learning curve. "VivaGel is in the fortunate position that it has been following other microbicides and has been able to learn from their experiences, even as they have been withdrawn for development. We are indeed following a strategy that has been refined in the light of previous studies," she says.

One problem with vaginal microbicides is the difficulty of testing them in the clinic, Lori Heise, director of Global Campaign for Microbicides adds, because they are user-controlled methods. "One has to rely on participants to accurately report their sexual behavior and use or non-use of the product," she says. "If a trial shows a low effect, you don't know if it is because the product didn't work or because people didn't use it consistently."

Most of the 30 products that have gone through clinical trials so far are known as early-generation microbicides. All these products share a nonspecific mode of action, either blocking viral transmission or maintaining an acidic pH in the vagina.

Renewed hopes ride on the promise of 'next-generation' microbicides—long-acting vaginal gels containing antiretroviral agents that target the virus directly. Gilead Sciences has developed a gel version of Viread (tenofovir) currently in a phase 2 trial of 900 women in South Africa. The Foster City, California–based biotech granted intellectual property rights to IPM and the Global Microbicide Project CONRAD, a Consortium for Industrial Collaboration for Contraceptive Research to develop, manufacture and, if proven efficacious, arrange for distribution of the product to 100 resource-limited countries (**Table 1**). IPM will use its support from the Gates Foundation, and DFID, to bring antiretroviral-based technologies into approximately nine new clinical studies. The IPM's most advanced microbicide candidate is dapivirine, a nonnucleoside reverse transcriptase inhibitor, used in vaginal gels and rings, with a phase 3 efficacy trial planned for 2011. But the partnership "will be pushing ahead with its development efforts around other microbicide candidates, including maraviroc and tenofovir gel," says Pamela Norick, a spokesperson for IPM. Selzentry (maraviroc) is a chemokine (C-C motif) receptor 5-blocker developed by Pfizer of New York, and the latest approved treatment for HIV.

Despite a patchy track-record, early microbicide candidates are still in the game. Sheena McCormack, a clinical epidemiologist with the UK Medical Research Council, who is involved in a phase 3 trial for PRO2000, also believes recent phase 2 results are a positive sign. "We are quietly excited," she says. The real indicator, McCormack says, will be the outcome of the phase 3 trial, which has over 9,000 women enrolled compared with the latest PRO2000 trial that had about 3,000 women. The results will be announced towards the end of the year.

McCormack fully understands why pharma has been unwilling to invest in the field. "Pharmaceutical companies got on board for the vaccines, which is a prevention market they know and understand," she says. Although there is a history of vaccines as key players in controlling infection, there have never been examples of topical products to prevent viral transmission. But microbicide research is less complex than vaccine development, and taking into account the profoundly disappointing trials of HIV vaccines, it is essential to explore several avenues for HIV/AIDS prevention. "Bill Gates could see that vaccines were a long way away, they were in the early product development line, and he recognized that microbicides were in the late-development stage," says McCormack. In addition to safety trials, the IPM will be conducting market research to assess the acceptability of vaginal tablets, films and soft gel capsules to users in Zambia, Tanzania, Mozambique and Burkina Faso. "Even the most potent and safe microbicides will not stem the pandemic unless women and their male partners will use them, so it is vital to determine preferences in the regions where women are at the greatest risk for infection," says IPM's Norick.

Samukeliso Dube, African program leader for Global Campaign for Microbicides, thinks it is absolutely essential to provide women with options to control their risk of infection. "Women in particular, have to rely on their partners to use a male condom, and in many parts of the world power dynamics within sexual relationships make this negation process difficult."

Nayanah Siva *London*

IN their words

"It seemed like an opportunity to bring a lot of money into a field that had a lot of promise and I don't think that's hype; I just think that's a matter of time."

Harvard's George Church, a cofounder of Cambridge, Massachusetts–based Codon Devices, which was launched with fanfare in 2004 but abruptly closed its doors in March. (*Nature*, April 16, 2009)