The relentless effort to curtail the HIV pandemic continues as researchers aggressively investigate alternative prevention tools.

A global, large-scale collaborative project involving world-renowned scientists is underway that seeks to cultivate combinations of highly active specifically targeted microbicides for vaginal and rectal application, known as CHAARM.

The CHAARM project, which stands for Combined Highly Active Anti-retroviral Microbicides, aims to explore the microbicide potential of protease inhibitors and will test them in combination with inhibitors of HIV-1 reverse transcriptase, integrase or fusion inhibitors, using a number of highly developed drugs. The purpose of this is to develop new microbicides and research new targets that would focus on inhibition of HIV-1 at rectal and vaginal mucosae.

“The CHAARM project has a central core laboratory testing set up enabling testing and comparisons of large numbers of different compounds,” says Dr Anna-Lena Spetz, Associate Professor at the Center for Infectious Medicine at Karolinska University Hospital in Stockholm, Sweden, a partner in the CHAARM project. “Hence, the CHAARM project enables involvement of researchers that (have) discovered new compounds with anti-viral activity and their drugs will be tested in a pre-clinical setting for use as microbicides.”

The CHAARM consortium includes over 30 partners from around the world, involving participation of public and private organizations, largely funded by the European Commission. Many of the participants have been involved in microbicide projects before, such as the European Microbicides Project (EMPRO), therefore giving them increased efficiency and adapting a systematic standardization of tools and techniques that can be used in CHAARM.

“It would be very difficult for each investigator to set up the efficacy and safety tests required to develop the drugs further,” says Dr Spetz.

First generation candidates such as nonoxoynol-9, Pro 2000 and Carraguard all failed to show effectiveness in reducing the transmission. As a result of these setbacks, there is increased pressure on finding new promising candidates from the second-generation microbicide products that can move forward in the efficacy trials.

Funding Difficulties

In addition to the challenge of finding promising microbicide candidates, as is a common barrier for research institutions developing a "public health good", there is little economic self-interest for organizations to provide funding for microbicide research, placing microbicide research in a financially vulnerable position.

"These funding bodies do not have infinite resources," said Dr Oliver Hartley, biochemist and professor in the University of Geneva's faculty of medicine. "A potential concern is that attractive new microbicide products validated through the CHAARM program might experience significant delays in clinical development because the necessary funds to move further are not available."

As is the case with the CHAARM project and most other research projects in this sector, they largely rely on funding from the public sector, government grants and non-profits. This has created a challenge for developers to sustain sufficient financial commitment to research and development of microbicides.

"Microbicides, like most public sector funded projects are always at a critical time point," says Mark Mitchnick, CEO Particle Sciences, Inc., a USA based pharmaceutical company.

"Developing drugs is a hard business," adds Mitchnick, who served on the advisory board for EMPRO.

Particle Sciences is one of the private companies involved in CHAARM. With the lack of involvement from private companies and pharmaceutical companies in microbicide research, the responsibility of funding has fallen largely on public institutions, government organizations and non-profits. The CHAARM project received about 70% of their funding from the European Commission.

"Maintaining focus and the attention of funders is a real challenge since progress can, from the outside, seems slow – even when things are moving well in terms of drug development," says Mitchnick.

Drug development is rather complex and expensive; however, the potential profit for microbicides is promising once next generation products are successfully developed.

A Changing Direction in Microbicide Research

With the obstacles and discoveries made with the first generation microbicide trials and restricted funding, the researchers in CHAARM have a hopeful direction with this research project.

Professor Robin Shattock, a Professor of Cellular and Molecular Infection in the Department of Cellular and Molecular Medicine at St George's University of London, UK, says the virus will be targeted more specifically with more emphasis being placed on blocking the infection of target cells.

The discoveries have led the field to move microbicides from being strictly at the time of exposure product, to be more prior to exposure and sustained delivery.

“It has also led to the field having to prioritize new formulations that maximize adherence to give the best possible chance of showing efficacy in a clinical trial,” said Professor Shattock while giving a speech at the International Microbicide Conference 2010 in Pittsburgh, Pennsylvania, USA. “Then it has led to increasing emphasis on combination products.”

“Not only to ensure that any microbicide will hit the widest possible diversity of virus, but also potentially to reduce the risk of resistance,” he added.

The use of combination anti-retrovirals is standard in HIV treatment and is used as post-exposure prophylaxis in developed countries for the management of individuals exposed to HIV occupationally and through sexual exposures. Nonetheless, the use of combination products in the project is a key aspect, primarily because they will increase the barrier to the development of resistance and may also improve efficacy.

“It is logical to use combinations of agents with potent anti HIV activity but which act through slightly different mechanisms with the aim that they provide synergistic protection and a higher barrier against resistant HIV strains,” said Dr Georgina Morris, HYMS (Hull York Medical School), Centre For Immunology and Infection, University of York and a member of the York HIV Research Group.

“The ideal candidates would have a long duration of action in tissues, be highly potent and have a high barrier to drug resistance,” said Dr Morris.

Microbicide candidates that will enter clinical trials will be selected based on several factors: the best class of inhibitor, potency, selectivity, stability, stage of development, resistance levels and ease at which they are able to be formulated in combination.

The CHAARM project will continue to investigate protease and proteasome inhibitors as potential microbicides as well as focusing on non-nucleoside reverse transcriptase inhibitors, specifically Dapivirine and the nucleoside analog reverse transcriptase inhibitor Tenofovir. In addition, new small molecule inhibitors of HIV-1 fusion will be developed as microbicides together with novel protein and peptide inhibitors based on CCR5 ligands such as RANTES derivatives.

"NNRTIs such as dapivirine are ideal with respect to half-life and potency but have relatively low barriers to resistance," said Dr Morris. "Darunavir is one of the most potent ARVs currently available and, as a protease inhibitor, has a high barrier to resistance, Combinations containing both PIs and NNRTIs are therefore very promising."

Future of the CHAARM Project and Microbicide Research

If CHAARM researchers succeed in developing an effective microbicide against HIV, it would have a major impact not only in the field, but also on sexual and reproductive health in general.

Even if microbicide products show promise as preventative options for reducing HIV transmission, they are not seen as an individual solution, but rather as products that will be used in addition to other preventative methods.

Although the CHAARM project is only a few months into its research, being a five-year program starting January 2010 and lasting until December 2014, there is a sustained level of anticipation of the results.

"In July this year the CAPRISA 004 trial yielded the first clearly positive results in a microbicide efficacy trial, providing significant momentum to the field," said Dr Hartley. "The CHAARM project now has the opportunity to build on this success, hopefully contributing to the development of a new microbicide product capable of making an impact on the HIV epidemic."

Project website:
www.chaarm.eu

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