ANTI HIV MICROBICIDES
#3204

General Information

Full Title

Anti HIV Specific Microbicides on the basis of Polyoxidonium

Tech Area / Field

- BIO-IMU: Biotechnology and Life Sciences / Immunology
- BIO-CGM: Biotechnology and Life Sciences / Cytology, Genetics and Molecular Biology
- BIO-MIB: Biotechnology and Life Sciences / Microbiology
- BIO-PAB: Biotechnology and Life Sciences / Public Health

Status

12345678 Submitted to Parties for Board Decision

Project Manager

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Leading Institute

Institute of Immunology

Supporting institutes

- Institute of Immunological Engineering

Collaborators

- US Department of Health & Human Services / National Institute of Health / Institute of Child Health and Human Development / Section of Intercellular Interactions

Project Summary

This project aims to study anti-HIV activity of polyoxidonium and to develop based on polyoxidonium anti-HIV specific vaginal microbicide for prevention of sexual HIV transmission.

The global AIDS pandemic continues to spread rapidly. The world urgently needs both an HIV vaccine and a micribicide. The development of an AIDS vaccine, however, is proving to be a lot more challenging than many had expected. Most HIV transmission occurs through sex. Use of vaginal microbicides, which provide a low-cost method, controlled by women, is one of the ways to prevent HIV sexual transmission. WHO/UNAIDS consider the development of microbicides with anti-HIV activity as the quick and efficient way to control HIV/AIDS spreading. Effective microbicides could save millions of lives.

Microbicides are any topical agent that inactivates or kills the pathogen, physically blocks its attachment to susceptible target cells, supports natural defenses, or prevent its more widespread dissemination from target cells. A topical microbicide would act as the first barrier to HIV infection.

In order to prevent HIV transmission, a microbicide must:

- Inactivate the virus in the vagina (the principle of surfactant, e.g. nonoxinol-9, and acidifying microbocides, as well as microbicides based on certain antibiotics and HIV antibodies); and/or
- Prevent the virus from attaching/fusing with its cellular targets (charged polymer microbicides, as PRO 2000 and some peptides work by this mechanism); and/or
- Accumulate in the target cells and block viral replication if the virus manages to enter (anti-retroviral drugs, as Tenofovir).

Clinical trials of the surfactant nonoxinol-9, in several formulations marketed for many years as spermicidal contraceptives, have demonstrated that this substance fails to protect against HIV, probably because it damages the vaginal lining which, when intact, acts as a barrier to HIV infection.

Thus, one of the challenges in the microbicides development is to support a healthy vagina.

Hence, *the aim* of the project is the study of polyoxidonium as possible anti-HIV agent and the development based on polyoxidonium anti-HIV vaginal microbicid for prevention of sexual HIV transmission. Taking in account the previously determined characteristics of polyoxidonium this substance is expected to be efficient for supporting healthy vagina and the epithelium lining and even it’s healing.

Polyoxidonium (PO), water-soluble co-polymer N-oxide-1,4-ethyl piperazine and (N-carboxy-ethyl)-1,4-ethylene piperazine bromide has been developed at the Institute of Immunology and has been shown to be the potent and safe immunomodulator. PO has been approved for use as immunomodulator and as a component of vaccines (carrier-immunostimulator). Currently, PO is being used in vaccines “GRIPPOL” (anti-influenza), anti-typhus, brucellosis, HIV candidate vaccine “VICHREPOL”. The safety of PO (including parenteral administration, 5-10-20 injections/course) has been shown in multiple studies, thus shortening the time of project completing.

The overall goal of the project is to study anti-HIV activity of polyoxidonium and to develop based on polyoxidonium anti-HIV specific vaginal microbicide for prevention of sexual transmission of HIV.

In proposed research, immunostimulatory and antiviral activity of PO will be studied. Anti-HIV activity will be evaluated in vitro (by cell-free and cell-associated assays and viral binding-inhibition assay), using cell lines, primary cultures and *ex vivo* tissue explants. Immunostimulatory activity of PO (cytokine profile and level) will be evaluated using several in vitro cell models. Regenerative (wound-healing) activity of PO will also be assessed. Vaginal irritation will be assessed using a rabbit vaginal irritation assay. Safety of PO *in the regimen of regular long-term (over months or years) prophylactic use* will be determined using animal model. *These last tests will be performed under the contract with American party, using their facilities*. All ex vivo model testing with explants will be done by US collaborators while technology is being transferred to Russian investigators. Testing of PO in the explant model and in PBMCs will be performed by US collaborators.

Screening data for anti-HIV activity will be confirmed by US collaborators as their contribution to the project (besides this work done by Russian team in Russian institutes and in the US partner's lab.).

Training in the USA of the Russian personnel in the laboratories of American collaborators represents the important part of this proposal. Main goal of this training is to transfer to Russia ex vivo culture method and RVI. Additional aims are to bring the procedures to the same standard in order to obtain reproducible, reliable and comparable data. Especially this relates to the detection of HIV-1 p24, cytokines and chemokines. Standard test procedure for the detection of HIV-1 p24 antigen will be established and agreed with American partner. Attempts to fit Quality Assurance Program will be made.

These studies will serve as a basis for the development of anti-HIV microbicide, capable 1) to support and mobilize normal vaginal anti-HIV resistance factors due to immunogenic and regenerative activity of PO and 2) to prevent HIV transmission due to preventing virus entry.

At the project conclusion we expect to proceed to the following: 1) evaluation of PO in monkeys and in human trials; 2) assessment of the combination of PO with other anti-HIV substances; 3) assessment of PO as potential rectal microbocide is also proposed.

It is proposed, that, upon this project completed, it will be followed by product development. Pilot production will be organized. The technology will be transferred to biomedical plants, and product produced in strict accordance with GMP standards under the supervision of the authors of this proposal.

The project will be executed by a group of experts (virologists, immunologists, chemists, biochemists) with long-term experience in the field and up-to-date methods and technologies. The project investigators have experience in designing, synthesis and investigation of anti-viral activity of different substances, including those with immunomodulatory activity, and those that block different stages of HIV life cycle. They have experience in conducting pre-clinical and clinical trials; search and study of

novel anti-HIV substances; product development and manufacturing. The applicants have a long-term experience of working with HIV, including HIV isolation from clinical samples and biological characteristics of isolates. They are authors of the pioneer works on search of the new potential anti-HIV preparations, the study of the mechanisms of action of variety anti-HIV agents, as well as the development of new approaches to assessment of antiviral activity. Applicants have experience in detection of HIV genome in different biological sources including semen and are co-authors of the development of those assays. The project investigators have more then two decades experience in the study of immune activity and conducting clinical trials of vaccines and therapeutics, as well as the development and manufacturing of diagnostic kits, vaccines and pharmaceuticals. They have developed the HIV vaccine candidate "VICHREPOL" (preparation contains PO). Pre-clinical trials by Russian Regulatory Authority (L. A. Tarassevich State Institute for Standardization and Control of Medical Biological Preparations) have been successfully completed, and a Phase I clinical trial is about to begin (approval of RF Ministry of Health obtained). Applicants have developed vaccine against influenza, "GRIPPOL", which is currently manufactured, which contains PO, vaccines against typhus and brucellosis. They developed an HIV diagnostic kit "PEPTOSCREEN-2" and organized manufacturing of the kit in accordance with GMP standards. The project investigators have an experience in executing joint international project (Fogarty, NATO).

Both Russian institutes, participating in the project, have an experience in executing ITSC projects.

American collaborators,

- Dr. L.B. Margolis, is the author of original method ex vivo culture of blocks of living human tissue (explants),
- Dr. Reichelderfer is a leading expert in microbicides and an author of numerous papers in this area of research.

All the proposed studies and trials will be conducted in compliance with the laws and legislations of the Russian Federation and the United Stated of America.

The Russian biomedical scientists could make valuable contribution to the solution of global problem in the fight against AIDS. Facilities of Russian bio-medical plants could ensure the cost-effective microbicides production, with lower costs when compared with Western countries. The lower cost will make products available for African and Asian countries, where AIDS epidemic spreads rapidly and sexual HIV transmission accounts for the vast majority of HIV-1 infections. In Russia, suppositories are being widely used in gynecology and proctology. Formulation and technology of production of suppositories for delivery of biologically active components, such as hormones, lactobacteria, antiseptics, are well developed in Russia, and the way of administration is acceptable for the population, including representatives of at-risk groups.

The project meets ISTC goals and objectives. It will give scientists from the Institute of Immunological Engineering, who fulfilled earlier the State orders of the Ministry of Defense, the possibility to redirect their scientific interests in pacific goals and to apply their experience for carrying out the investigation on the development of vaginal anti

HIV microbicide.

The execution of the project on the development of effective and affordable microbicide could be a new example of successful cooperation of Russian and American scientists, designated to the solution of the global scientific, medical and social problem of great importance and urgency – defeating HIV/AIDS pandemic.