Rotavirus Vaccine: NIH Office of Technology Transfer

The National Institutes of Health (NIH), as part of the U.S. Public Health Service (PHS), is dedicated to improving the public health of individuals worldwide through innovative research and the funding of critical medical research programs. Immunization against rotavirus disease is an important public health initiative supported by several organizations worldwide. This case study describes the partnerships between PHS and institutions in Brazil, China, India, and the United States that have been established to facilitate development of a safe, effective, and affordable vaccine for arresting the overwhelming mortality associated with rotavirus infection in the developing world.

PARTNERS

Partners in the rotavirus vaccine project are:

- from government: the National Institutes of Health/U.S. Public Health Service
- nonprofit organizations: Fundação Butantan (Sao Paulo, Brazil), Chengdu Institute of Biological Products (Chengdu, China), and Wuhan Institute of Biological Products (Wuhan, China)
- for-profit companies: Aridis Pharmaceuticals (United States), Bharat Biotech International, Ltd. (Hyderabad, India), Biological E., Ltd. (Hyderabad, India), Shanta Biotechnics, Ltd. (Hyderabad, India), and Serum Institute of India, Ltd. (Pune, India)

EPIDEMIOLOGICAL FEATURES OF ROTAVIRUS

Rotavirus is the leading cause of severe dehydrating diarrhea in infants and children worldwide. According to a report issued by the World Health Organization (WHO), each year, the disease is responsible for about 25 million clinic visits, two million hospitalizations, and between 352,000 and 592,000 deaths in children age five and under. As one can imagine, the worldwide economic burden associated with rotavirus disease is staggering, exceeding $1 billion each year in medical costs. Children in developing countries are disproportionately at risk of dying from rotavirus-related infection. In India alone, rotavirus is blamed for the deaths of approximately one out of every 250 children each year, and in China, the disease accounts for more than 34,000 deaths per year. This rotavirus-associated mortality is due in part to inadequate sanitation and to inadequate access to intravenous rehydration therapy in poor countries.

THE TECHNOLOGY

The human-bovine reassortant rotavirus vaccine is an invention of Dr. Albert Kapikian and his colleagues at the National Institutes of Allergy and Infectious Disease (NIAID) of the NIH. The invention was further developed through collaboration with Wyeth Pharmaceuticals. The vaccine technology is based on multivalent immunogenic compositions comprising four human-bovine reassortant rotaviruses and involves the insertion of the gene-encoding VP7 protein of G1, G2, G3, and G4 human rotavirus strain into a bovine rotavirus backbone. These VP7 serotypes represent the clinically most prevalent human rotavirus serotypes. Additionally, the basic quadrivalent vaccine formulation can be augmented with G9 and G8 strains (or one of these additional strains for a pentavalent formulation) to make a hexavalent formulation. Serotype 9 (G9) has emerged as an important strain in Latin America and the most important

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strain in Brazil, whereas G8 is prevalent in many African countries.

Originally, the human-bovine reassortant rotavirus vaccine was intended as a second-generation rotavirus vaccine. It was developed alongside the human-rhesus reassortant vaccine, RotaShield, an earlier invention of Dr. Kapikian that was commercialized by Wyeth following U.S. Food and Drug Administration approval in 1998. RotaShield was voluntarily removed from the market in 1999 after the vaccine was suspected of being linked to an increased risk for intussusception in children. After the withdrawal of RotaShield from the market, interest in the human-bovine reassortant technology increased, which led to multiple applications for commercial licensing as detailed below.

LICENSE AGREEMENTS

Published reports and presentations by NIH NIAID investigators generated significant interest in the human-bovine rotavirus vaccine technology from companies and institutions worldwide. In 2005, eight organizations, one in the United States and seven based in the developing world, were granted licenses from PHS to manufacture and distribute the rotavirus vaccine. The licensees are U.S.-based Aridis Pharmaceuticals; Fundação Butantan, a Brazilian government institution; Bharat Biotech International, Biological E., Ltd., Shantha Biotechnics, Ltd., and Serum Institute of India, Ltd., all India-based companies; and Chengdu Institute of Biological Products and Wuhan Institute of Biological Products, both funded by the government of China. The vaccine technology is covered by issued patents (and pending patent applications) in the United States, Europe, Canada, Japan, China, India, Korea, Brazil, and Australia, thus NIH decisions regarding the license agreements were based on thorough evaluation of the applicants and their capabilities with regard to vaccine research and manufacturing. The license agreements with all parties are based on territorial rights and include both rights for the intellectual property and to biological materials. The biological materials include all the vaccine strains, as well as the analytical reagents necessary to develop the vaccine.

Butantan was awarded an exclusive license to practice the invention for development of a rotavirus vaccine in Brazil and Latin America. In cooperation with the Brazilian Ministry of Health, Butantan plans to introduce the vaccine into Brazil's child immunization program, which provides free vaccines for all children of Brazil. Similarly, Chengdu and Wuhan will manufacture and supply the rotavirus vaccine to China's expanded program of immunization (EPI). The Office of Technology Transfer (OTT) at NIH granted to the four Indian companies licenses to the IP rights in India and rights to manufacture and distribute the rotavirus vaccine in India and other developing countries, excluding Brazil and other Latin American countries and China. Finally, Aridis was granted an exclusive license to IP rights covering the rotavirus vaccine in the United States, Europe, and Canada. By using this multipronged approach and carving out territory-specific agreements, PHS ultimately set the stage for global distribution of the rotavirus vaccine. The terms of the agreements were structured according to each licensee's mission to provide free or affordable vaccines to children in their specific territories.

PROGRESS, CURRENT STATUS, AND GOALS

The human-bovine reassortant rotavirus vaccine is expected to reach the market in developing countries in five to six years. All the licensees are currently in a stage of organization, preparing all the necessary facilities and infrastructure for manufacturing the vaccine and for clinical trials. The licensees plan to receive training in the technology involving the vaccine at the laboratory of Dr. Kapikian at NIH. It is anticipated that the Codevelopment will include collaboration with the NIH. OTT staff was recently notified by its partners and the staff of the Bill & Melinda Gates Foundation that the latter will support partial development of clinical trial procedures for screening the technology at specific institutions in developing countries. ■

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