Typhoid Vaccine: NIH Office of Technology Transfer and the International Vaccine Institute

This case study illustrates the important role that the Office of Technology Transfer (OTT) of the National Institutes of Health (NIH) plays on behalf of the U.S. Public Health Service (PHS) in assisting the mission of global health organizations to alleviate health problems in developing countries. In this case a transfer of biological materials, as well as know-how from PHS, assisted the International Vaccine Institute (IVI) in its mission of combating typhoid fever in developing countries.

The International Vaccine Institute is an international organization that was established through the initiative of the United Nations Development Program (UNDP) under the Vienna Convention of 1969. Through March 2007 35 countries and the World Health Organization (WHO) have signed on to the convention. The institute is governed by an independent board of trustees and is located in Seoul, Korea. The IVI was founded on the belief that health in developing countries can be dramatically improved by the development, introduction, and use of new and improved vaccines and that these vaccines should be developed through a dynamic interaction among science, public health, and business entities. IVI contributes to the reduction of vaccine-preventable diseases in developing countries through collaborative research that generates the evidence needed for the rational introduction of new vaccines. IVI's mission is supported by programs of basic and applied laboratory research, product development, training, and technical assistance.

Typhoid fever is a major cause of morbidity, with an estimated global prevalence of between 16 million and 30 million cases each year. Typhoid fever is blamed for 500,000 to 700,000 deaths each year. A safe and efficacious vaccine against the disease is the most effective way to combat this deadly disease. Development of such a vaccine has therefore become one IVI's highest priorities.

THE TECHNOLOGY

The three currently licensed vaccines against typhoid fever—attenuated Salmonella typhi Ty21a, killed whole cell vaccines, and a Vi polysaccharide—all have drawbacks such as side effects and limited efficacy, in particular in children under five years of age. A better vaccine is therefore necessary to combat the global issue of typhoid fever, and IVI has been particularly interested in exploring the potentials of conjugate vaccines. Following this line of pursuit, IVI requested the help of Dr. John Robbins at the NIH, who is a recognized world leader in the area of conjugate vaccines and is in possession of the know-how and the biological materials necessary for making such a vaccine. Robbins developed a Vi conjugate typhoid vaccine in the late 1990s (U.S. patent No. 6,797, 275). The vaccine has been studied in China and in Vietnam, with the results of the clinical studies in Vietnam published in the vaccine literature (Lin, et al, 2001, N Engl J Med. 344(17):1263–1269). While an effective vaccine against Salmonella typhi needs to increase serum antibodies eight-fold after immunization, the conjugate vaccine of Dr. Robbins' invention increases antibodies 48-fold in adults, 252-fold in five-to-14 year-old children, and 400-fold in two-to-four year-old children. Thus, it is a highly effective vaccine, particularly for children, and should be valuable both in endemic regions and as a travelers' vaccine. In addition, administration can be combined with routine immunizations.

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THE IVI LICENSE AGREEMENT WITH NIH

Under a biological material license agreement (BMLA), the NIH provided to IVI the necessary components of the vaccine as well as samples of the final vaccine composition. The conjugate vaccine consists of two parts, the capsular polysaccharide of *Salmonella typhi* Vi and a carrier protein, a nontoxic recombinant exoprotein A (rEPA) from *Pseudomonas aeruginosa*, that are linked together via an organic dihydrazide named adipic dihidrazide. An alternative carrier protein, currently being used by IVI, is diphtheria toxoid (DT). The DT protein is provided to IVI by the Lanzou Institute for Biological Products in China and by Shantha Biotechnics in India. The license agreement with the NIH also provided IVI with critical reagents for the analytical work required for assessing vaccine quality.

Significantly, the terms of the agreement were tailored to IVI's global public-health mission and nonprofit status. The agreement allows sublicensing and acknowledges IVI's sublicensor-sublicensee relationship with BioFarma, a leading public-health institution in Indonesia.

After the execution of the agreement with the NIH in February 2005, collaboration between the Robbins laboratory at NIH and IVI was established. The Robbins laboratory is continuing to assist the IVI in its development of the vaccine.

PROGRESS, CURRENT STATUS, AND GOALS

By now IVI has established reliable procedures and a scaled-up protocol for production of the vaccine. IVI has optimized the analytical assay methods required to assess vaccine quality. Furthermore, IVI has established one formal partnership with a developing-country manufacturer. A second manufacturing company has expressed interest in a partnership.

IVI's plans for the next year include:

- Produce three consecutive ten-liter lots of Vi vaccine to demonstrate consistency of manufacture at IVI. Demonstrate that these lots meet WHO requirements for Vi vaccine.
- Transfer Vi polysaccharide production technology to at least one developing-country vaccine manufacturer.
- Prove that the Vi-DT conjugates produced at IVI meet the standards of quality set by NIH.
- Demonstrate satisfactory immunogenicity of Vi conjugates produced at IVI.
- Scale up conjugate preparation process.
- Identify a GMP contract manufacturer for preparation of a clinical lot of Vi conjugate.
- Initiate the process of approvals for a Phase I clinical trial.
- Finalize assessment criteria for Vi conjugate (in process and final lot) and ensure that assays are in place and validated.
- Initiate the process of technology transfer to at least one developing-country manufacturer for the Vi-DT conjugate vaccine.

Throughout its development work, IVI has maintained close contact with WHO in order to ensure that the vaccine specification will be acceptable to WHO prior to the vaccine transfer. ■

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