NYU's Malaria Vaccine: Orphan at Birth?

A disagreement among sponsors clouds the future of an important medicine even before it's created

An odd thing happened last fall to New York University's (NYU) project for creating a malaria vaccine. Just as the technical prospects for a workable vaccine brightened, the prospects for getting it manufactured suddenly grew dim. The reason was that one of the lesser funders of NYU's research, the World Health Organization (WHO), could not agree with the proposed manufacturer, Genentech, on how to share the property rights.

Genentech wanted an exclusive license to market the vaccine, while WHO insisted that the company be given something less, based on the fact that WHO funding contracts contain a clause ensuring "public access" to the fruits of WHO-sponsored work. Although all the parties involved in this project say their differences will soon be worked out, they have reached an impasse in their negotiations. This became clear in December.

If this contretemps (for WHO insists it is not a dispute) is resolved, it could set a precedent for sorting out claims to complex bioengineering projects of this kind. It is also a test of the ingenuity of academic entrepreneurs. NYU must reassure not only its own faculty, but collaborators at other institutions that the decision to go commercial will not interfere with the sharing of research data. Finally, NYU's quandary reflects an old problem in tropical medicine—the tension between underdeveloped nations which need medicines and cannot make them, and the developed nations which can manufacture them but may not care to.

It is estimated that 200 million or more people suffer from malaria, nearly all of them living in underdeveloped tropical areas. (During the Vietnam War, it is said, more Americans were put out of action by malaria than by Vietcong.) Only a handful of commercial gene-splicing companies, such as Genentech, are able to carry out the clone-generated production of antigens on the large scale envisaged for malaria vaccine. These companies exist only in the United States and Western Europe. They are quite selective in the projects they launch, scrutinizing proposals, among other things, for profitability.

It is discouraging for an underdeveloped nation to find that its citizens' welfare may depend on a business decision made by an obscure company in California or Switzerland. Thus it is not hard to understand why WHO officials are reluctant to waive their rights to the malaria vaccine, something which, if it appears, will have been helped along by WHO financing.

The research that prompted these negotiations has been carried out at NYU under the leadership of Ruth and Victor Nussenzweig. Both started their work on tropical diseases at the University of São Paulo, in Brazil—their home until 1963. That year, Victor received a Guggenheim Fellowship, and both traveled to the United States. In their absence, Brazil was shaken by the generals' coup that deposed João Goulart. After a brief return to São Paulo, the Nussenzweigs moved to New York and settled at NYU, where in 1966 Ruth began the malaria project she has pursued ever since. She has now become head of the division of parasitology. Victor followed other interests in immunology, but has recently resumed work with Ruth on malaria.

The Nussenzweigs have collaborated with scores of researchers over the years, including those studying two different stages of malaria infection. The stage studied by the Nussenzweigs is the initial one, called the sporozoid stage, the form of the parasite when it is first injected into the body by a mosquito bite. The sporozoids migrate in minutes to the liver, where they establish an infection. Six to 12 days later, it bursts forth into the bloodstream in the merozoid stage, which produces the fevers, chills, and other symptoms associated with malaria. Later, some merozoids develop into a gamete form, which, if taken up by a biting mosquito, infects the mosquito.

The drawback with a plan that focuses on a sporozoid vaccine is that some believe it is an all-or-nothing proposition. If just one sporozoid survives the body's immune response (and a mosquito bite may inject several hundred sporozoids), a severe infection may ensue. Antibodies that attack the sporozoid do not affect the merozoid. Thus, the Nussenzweigs say that the ultimate vaccine will probably be designed to stop both the sporozoid and merozoid stages. Other researchers are working on a gamete vaccine as well, but its effects would be less dramatic. It would prevent the transmission of malaria from man to mosquito, reducing the disease by lowering the number of infected mosquitoes.

Despite its limitations, the attack on sporozoids is generating a lot of interest because it is moving rapidly toward a vaccine that may be practical to manufacture. Whether or not such a vaccine would be effective is another matter, something to be learned in clinical trials sponsored by the manufacturer. Louis Miller, who directs merozoid vaccine research at the National Institutes of Health (NIH), says for example that "everyone is excited" about the progress being made, and that "the Nussenzweigs are a couple of years ahead of us." They are farthest ahead, it seems, because of the work they have done with monoclonal antibodies and with gene-splicing.

The Nussenzweigs decline to talk about the latter because it has not been reviewed or published. They worry, they say, that disclosing any information could jeopardize papers now in preparation.

It is clear from the Nussenzweig's published work that they have identified a key sporozoid surface protein in several species of malaria, including those that infect mice (*Plasmodium berghei*), monkeys (*P. knowlesi*), and man (the lethal *P. falciparum* and the chronic *P. vivax*). They have shown that this protein is similar in all cases studied and that it helps the parasite infect its host. They have produced monoclonal antibodies that bind to these proteins, and shown them to be similar to antibodies that occur in animals with natural immunity to malaria. They have tested the antimalarial potency of the monoclonals in chimpanzees infected with human malarias. The antibodies were partly effective in preventing infection.

The work at NYU has gone well beyond this point, although the degree of progress is being kept confidential. On 12 February 1981, NYU filed a patent application which presumably describes a process for making a malaria vaccine. Associate Dean David Scotch says merely that it "covers the work done in the

Nussenzweigs' laboratory." It also covers collaborative work with Nigel Godson, an Englishman who chairs NYU's biochemistry department.

Although Godson began working with the Nussenzweigs 3 years ago when they "needed some work done with recombinant DNA," he and the Nussenzweigs have not published the results of their joint effort. Rumor has it that they have cloned the gene for the key protein of the monkey malaria (*P. knowlesi*). If this is true, it should be relatively easy to obtain clones for the two human malarias and to use them to produce pure antigens. (The importance of cloning the gene is that this makes mass production possible. The only source of antigen material until now has been from sporozoids removed laboriously by dissecting mosquito salivary glands.) The antigens, injected as a vaccine, produce an immune response that in theory will protect the vaccinated person against malaria.

When the patent was filed, Scotch says, NYU notified all its funding sources that a commercial venture was in the making. Among those notified were the U.S. Agency for International Development (AID), the principal supporter of NYU's malaria research, NIH, and WHO. "We felt that Genentech would be best equipped to collaborate on this project," Scotch says, "and we started having discussions with them." Draft agreements changed hands, and in July 1982, Scotch took a not-quite-completed text to Geneva to show to WHO. "They told me it was not satisfactory because it did not adequately protect the public sector. We agreed to meet again in September." Meanwhile, the NYU-based research moved ahead rapidly, apparently accomplishing some of the early gene-splicing work that Genentech was to have done.

In September, all the parties—NYU, Genentech, AID, and WHO—met in a room in the United Nations building. Genentech still wanted full rights to the vaccine. WHO insisted that some concessions be made to WHO. The parties separated, according to Scotch, by "agreeing to agree." So far, neither Genentech nor the university has come up with a solution.

In a formal statement issued in December, WHO indicated that it was up to Genentech, through NYU, to "make proposals designed to reconcile its perceived needs for exclusivity with the access rights to which WHO and AID are entitled by virtue of funding agreements."

Genentech's legal counsel, Brian Cunningham, says that the negotiations are "up in the air," and that the "ball is in their court." He adds: "Frankly, this is not the hottest item on the agenda." He could not recall any case in which Genentech agreed to make a product without obtaining exclusive marketing rights.

There are a few other obstacles to an agreement. AID and NIH are governed by a new patent law (PL 96-517) which took effect on 1 July 1981. It allows grant recipients to take out patents on government-sponsored work, provided the discovery is made after July 1981, and provided the government is allowed royalty-free use of the invention. Although the Administration has told the bureaucracy to encourage private patent filing, AID attorney Jan Miller sees a few hitches in this case.

First, there is the problem that NYU filed its patent in February 1981, before the effective date of the new patent law. The rights thus may remain with the government. It may be possible to smooth this over, if NYU petitions for greater rights, Miller says. That has not happened yet.

Second, Miller worries that if the NYU researchers join Genentech in a commercial project, they may be less willing than in the past to share data with AID's $30-million malaria research network. The terms of AID's funding agreement call for mutual and immediate sharing of data, and the Nussenzweigs are funded by AID through 1985. Scotch sees no problem here because the proposed contract with Genentech allows the company to keep NYU data confidential only for a period of 30 days—long enough to file a patent but not long enough to affect scientific communication. Miller, however, is not convinced that AID would get as much information under this scheme as in the past.

Third, Miller wonders whether AID's grantees would get access to clinical trial data if Genentech gets that far in developing a vaccine. Scotch says the question is not one that NYU can answer because the data will belong entirely to Genentech.

The bargaining over market rights has been discouraging, the Nussenzweigs say, because it puts their work in a bad light. As early as November 1980, Sidney Cohen, another leading malaria researcher at Guy's Hospital Medical School in London, wrote to *Nature* criticizing "some institutions" for "contemplating individually beneficial patent rights." Cohen argued that progress on a malaria vaccine was dependent to a great degree on cooperation among all researchers. He wrote that patent-seeking "already threatens to disrupt in part the complex web of collaborative work."

Only governments and charitable agencies will be able to buy the vaccine, for the people who need it cannot afford it. "Under these circumstances," Cohen asked, "can any institution justify a claim to benefit individually from a restricted aspect of work, however important, which contributes to the development of a malaria vaccine?" He called for a moratorium on patents and an international parley to arrange for data sharing. No such meeting has been held.

More recently, according to Scotch, there have been "innuendos" from other sources suggesting that the Nussenzweigs have a financial stake in the patent. This is not true, Victor Nussenzweig says. Income from the patent will be given to NYU to fund additional research in tropical medicine. It is emotionally draining, Ruth says, to be confronted with such harsh personal criticism. It dampens her enthusiasm.

The Nussenzweigs and Godson agree, based on their recent experience, that combining academic and commercial interests in a joint venture makes for a poor marriage. Realistically, however, they see no alternative for getting a vaccine manufactured.

Officials at NYU and the funding agencies are confident that they will overcome the legal obstacles that stand in the way of developing a vaccine. If they fail, they could end up with the world's most important orphan drug.

—ELIOT MARSHALL

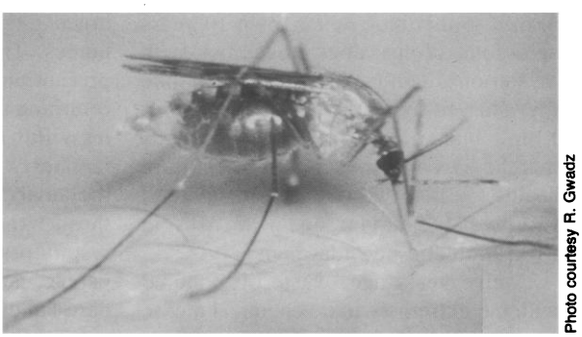

Photo courtesy R. Gwadz

Malaria carrier

Robert Gwadz raises infected Anopheles freeborni *like this at NIH in Washington. He ships thousands of them live to NYU each week, where they are dissected and the malaria sporozoids removed for experiments.*