Pesticide resistance among mosquito populations and ineffective mosquito control programs have hindered efforts to reduce viral transmission. Consequently, arthropod-borne diseases are increasing worldwide. Novel biological strategies adopted by Barry Beaty, director of AIDL, and colleagues aim to "immunize" mosquitoes against viral parasites, and thus reduce their vector competence. They have derived an antisense RNA based on the RNA genome of the pathogen, and have used that to block replication of the virus in mosquitoes. The ultimate goal is to engineer a virus-resistance gene into the vector, creating transgenic mosquitoes that constitutively express the gene and pass the resistance trait on to future generations, rendering them harmless.

The mosquito *Aedes aegypti* transmits dengue viruses to humans via its saliva. The virus replicates within the mosquito and spreads to various organs, including the salivary glands. The dengue viral genome encodes 10 proteins and is translated as a single polyprotein. Antisense RNA complementary to the 5′ end of the viral genome will, therefore, affect translation of all downstream sequences. Beaty et al. (*Science* 272:884-886, 1996.) demonstrated that inoculation into the mosquito thorax of recombinant Sindbis virus containing appropriate antisense RNA coding regions prevents the replication of dengue virus (which was inoculated at the same time) in the salivary glands. Expression of antisense sequences was verified. However, Sindbis—which is innocuous to mosquitoes but a human pathogen—is a model system only.

To adapt this technology for field use, the researchers have clearly needed to move away from using Sindbis virus as the delivery vehicle for the antisense molecule. Now they are experimenting with a host-restricted parvovirus—a natural pathogen of *Aedes* that is transmitted through mosquito eggs, but does not infect humans. "We're showing that we can use the parvovirus to express genes and gene sequences right now, and we're about to put the dengue constructs in and see if they will inhibit infection," says Beaty.

In similar work, the researchers have used a recombinant Sindbis virus to express sequences of LaCrosse virus in *Aedes* triseriatus (*Proc. Natl. Acad. Sci. USA*, in press). The LaCrosse virus causes a form of encephalitis in humans. Of the 12 different LaCrosse genome fragments introduced into Sindbis, four have been able to interfere with subsequent LaCrosse viral infection and replication. One antisense sequence that has been particularly effective against homologous virus challenge also inhibits infection by heterologous viruses that have a high degree of sequence homology with that of the LaCrosse virus.

Beaty and his coworkers are also using the recombinant Sindbis strategy to knock out gene expression in mosquitoes, understand gene function, and identify specific targets for vector control. Efforts to prevent disease-transmission by controlling mosquito populations have failed. "If you eradicate one [mosquito], you usually have another come in to fill the niche. Nature abhors a vacuum," says Beaty. "There's something maybe to be said about looking at this [approach] as making mosquitoes only a pest population instead of a vector population."

Vicki Glaser

Summertime, and the living is sneezy

This allergy season, pharmaceutical companies are offering the usual fare of over-the-counter antihistamines, while irritating pollens, molds, and grasses waft on the breeze. For two biotechnology companies heading toward the billion dollar allergy marketplace, Tanox Biosystems (Houston, TX) and Genentech (South San Francisco, CA), patent disputes are also in the air. In August, the two companies are scheduled to go to court to try to settle the suits and countersuits surrounding their closely related monoclonal antibody (Mab) products that block the IgE cascade—the root cause of allergy.

IgE binds to specific receptors on the surfaces of mast cells and basophils, where cross-linking by the allergen and the resultant receptor aggregation lead to the release of histamine, leukotrienes, and other allergic-response effectors. Theoretically, eliminating the binding would, in turn, quell the effects of hay fever and some of the symptoms of asthma. In 1989, Tse Wen Chang of Tanox identified the IgE receptor-binding region that attaches to allergen effector cells. This discovery led to a scientific collaboration between Tanox and Genentech, the souring of which has led to the current patent dispute.

Both of these companies are developing chimeric monoclonal antibodies against the IgE receptor regions. The molecules do differ: the Tanox compound has mouse variable regions joined to human constant chain while Genentech's antibody has complementarity-determining regions from the mouse that are embedded in a human framework.

Back in December 1993, Tanox sued Genentech for breaching an agreement not to develop a product after scientific collaboration that involved Tanox sharing the IgE technology with them. In a countersuit (filed in January 1994), Genentech challenged Tanox's right to produce the chimeric antibody by claiming it has infringed the "Cabilly patent," a broad patent covering chimeric immunoglobin compositions.

The dispute is only noteworthy because the products look like they might very well be worth fighting over. Tanox—backed by the pharmaceutical giant Ciba-Geigy (Basel, Switzerland)—and Genentech are both currently gearing up for phase II clinical trials of the products for asthma. Tanox is about to conduct a 400-patient study, whereas Genentech has already demonstrated that its product lowers serum IgE levels and is currently recruiting for the second part of a phase II study. According to Daniel Adelman, clinical scientist at Genentech, relief from the symptoms of asthma occurs in patients whose IgE levels fall below detectable levels.

Previously, the Tanox product performed well in phase I and II clinical studies for hay fever sufferers. According to Chang, the results of the double-blind, phase II, hay fever study showed a dose-related response: High-dose patients experienced fewer symptoms and used fewer "rescue" medications. Genentech's rhinitis phase I results were less successful. Robert Fick, senior clinical scientist at Genentech, reported that its antibody reduced IgE serum levels, but the reductions were not usually low enough to produce significant clinical benefit.

Neither of the products from Tanox and Genentech will progress to later-stage trials for hay fever any time soon. Tanox needs to develop a commercial manufacturing process for the antibody before it proceeds to phase III trials. "Meeting the regulatory requirements will take several years. . .," Chang says. And Genentech plans to discontinue rhinitis trials for the moment and will focus instead on the more promising asthma studies.

Barbara Nasto

Barbara Nasto is a science and medicine writer with Nature Publishing Co. in New York.