Pure Gene-ius

Leading geneticist Alan Lambowitz, Ph.D., introduces introns, a breakthrough that may make gene therapy safe and effective against HIV.

November 1, 2000 By Maia Szalavitz

The momentous and widely heralded decoding of a "rough draft" of the human genome, announced in June, may well improve prospects for using gene therapy to treat human disease, including HIV. Up until now, though, successes have not only been rare, but one experiment actually proved lethal: Last year, a teenage boy died from an allergic reaction to a virus used to introduce genes into his body to treat a non-life-threatening metabolic problem. The good news is that recent work by Alan Lambowitz, PhD, director of the Institute for Cellular and Molecular Genetics at the University of Texas at Austin, and his colleagues may mark a turning point. One of the key problems in gene therapy has been how to safely transport the therapeutic genes into the right places in quantities large enough to make a difference. By using gene components called introns rather than potentially problematic viruses to insert the genetic material, Lambowitz's group has hit on a method that may overcome the failures and dangers of earlier approaches. Reporter Maia Szalavitz recently interviewed Lambowitz about the exciting possible applications of his team's work for treating HIV disease.

***POZ*: What are *introns*, and why are they important to your new method of gene therapy?**

Alan Lambowitz: In higher organisms, a gene consists of information sequences, called *exons*, separated by intervening sequences, called *introns*. Up to half of the genome consists of these introns. We don't know why these genomic parasites are there. But we do know they are harmless: When the DNA that the introns are in is used to make protein, they are transcribed and splice themselves out. All that remains is the information necessary to make the protein. Ironically, Group II introns, the type we're working with, may be ancestors of retroviruses like HIV. But when retroviruses insert themselves into the genome, they -- unlike introns -- *don't* splice themselves out and thus can cause harm.

In our recent work, we found a way to use a Group II intron to disrupt the gene used to produce CCR5, a receptor protein on the CD4 cell that allows HIV to enter and infect the cell. In the lab, we inserted into human cells both an intron and a copy of a CCR5 gene carried on a *plasmid* (a piece of DNA that carries genes from place to place). In this artificial situation, we demonstrated that the intron could find and attack its target -- in this case, the CCR5 gene.

But it remains to be seen if the intron will be able to insert itself into the actual chromosome (a more complex structure composed of two strands of DNA). We are working on doing this now.

What would this mean if it worked?

If we could disrupt CCR5 in chromosomes, we could generate a population of HIV-resistant CD4 cells. In principle, this could arrest the progression of disease, because while you would still have some infected cells, you could generate new resistant cells and repopulate the immune system with them. Conceivably, this could work permanently. And you wouldn't need to use a virus to get the genes into the cells -- you could micro-inject the introns into cells and then infuse them into the patient. Introns insert at precisely designated sites, so you can use them to introduce a new gene or disrupt existing ones.

You have also used introns against HIV itself.

Yes. You could, in principle, use introns to target any part of HIV. We are exploring applications that would target virus that has already integrated itself into human cells. The idea is to use introns to introduce an additional component that is active against HIV. It would essentially use HIV against itself: The HIV would be infused with the new introns and something called a ribozyme, which can destroy the virus' ability to reproduce. We have done this in plasmids, but again, we have to try it in chromosomes.

There are some barriers, but in nature, there is a very similar process. And if it works in chromosomes, you could treat virtually any genetic disease, cancer and a variety of DNA viruses (such as human papilloma-virus, hepatitis B and herpes viruses) -- all could be targeted by introns.

What are the dangers of this approach? Although people with defective CCR5 seem healthy, we really don't know whether disrupting it might be dangerous or whether introns themselves might cause side effects.

It's hard to assess potential dangers because we're not yet at the stage of doing gene therapy. In general, this mode of gene delivery would be safer because it is done on individual cells outside the patient and because it doesn't use viruses.

Where has your funding come from, and where do you see this approach going from here?

Introns are pretty esoteric, and we didn't expect them to lead to practical applications. So up until now our funding has mainly been basic-science grants from the National Institutes of Health. Recently, a company was formed to provide patent protection and pursue commercial applications. We really do think that introns have potentially wide uses -- although I can't put a timetable on it. But it's a sophisticated, clever mechanism and the possibilities are quite exciting.

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