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Commentary

Oligonucleotides Get a Face-Lift

It's been a long time coming for oligonucleotides. Long considered the peons of DNA synthesis—workhorses ensuring replication and mutagenesis at the proper sites—oligonucleotides are now themselves stepping into the limelight as possible new therapeutics. It's hard to believe their modest pasts. Can these little nucleic acid fragments, formerly cast off as mere genetic debris, be the solution to cancer? Viral infections? Cellular protein excesses of all shapes and forms? Retired molecular biologists are shaking their heads in disgust. "It was right under our noses . . . ," they mutter and cringe. Newly hired postdocs are racing back to their synthesizers claiming, "No, we're not making primers for PCR, we're designing the cure for AIDS!"

Perhaps it's a bit too soon to abandon the idea of safe sex, but maybe not too late to rearrange the investment portfolios. Don't bother with disclosure though; rumor has it the Office of Information and Technology Transfer has just allowed the patenting of adenine, guanine, cytosine, and thymine to some forward-thinking entrepreneur. To market the oligo to *Herpes* or c-myc, you'll have to buy the rights to the individual nucleotides—so best keep it under 20 bases and try to maximize the use of uracil.

Mechanism of action of these little ones? Quite straightforward. While the nucleus is off transcribing, they bind to messenger RNA and halt translation. Or when they really want to be bold, they just head straight for the DNA and form a triple helix, right there in the major groove. Transcription factors are left speechless and without a promoter on which to rest. Hoogsteen would be proud. The latest bunch making the scene are revisionist oligos, reliving the wild days when *tetrahymenae* took the law into their own hands and self-spliced their own RNA. Oligos are now donning a similar costume. They set their sitings on a messenger RNA, make contact, catalyze for the kill, and move on unscathed—without even a smoking gun. The best part is their inconspicuous nature. Any of these oligonucleotides could just as well be lunch remnants from some passing endonuclease as far as the cell is concerned. The elegance of science never ceases to amaze.

It won't be long until our cells catch on and fight back against the therapeutic effects of oligonucleotides. Nature has a funny way of doing that when scientists come up with good ideas. Perhaps our cells will start to form new membrane proteins. We'd probably call them oligopoliceosomes. I can almost picture them inserted and surrounding the nuclear/cytoplasmic pores, questioning all RNA's under 2 kilobases and without a 5′ cap. . . .

"Passport? Chromosome ID number? and where's your polyA tail?" they'll bark at an unsuspecting single strand.

"Me? Chromosome number 17, the small part. Officers, I'm just a wayward beta-globin intron on my way out of town."

"Ok, you may pass. But you better exocytose yourself with the next outgoing lysosome," and the protein gates will crank open and snap shut again. . . .

Yes, oligonucleotides are finally getting the heyday they deserve. Oligo journals and symposia are springing up almost daily. Physicians from all over the world are now needing to dust off their textbooks and bone up on their biochemistry. Who would have thought? Maybe *Time* magazine's 1993 Man of the Year will be the oligo targeted to the HIV *tat* gene. . . .

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