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No payoff without delivery

In his novel *White Noise*, Don DeLillo envisions a slow-release capsule to deliver a drug that "cures" the user of her fear of death. It is doubtful that even the most starry-eyed avatars of functional genomics—and its seemingly endless supply of drug leads—anticipates such a new medicine. What can the rest of us realistically expect in the postgenomic era, when drugs are developed based upon gene sequence and expression rather than upon symptom and phenotype?

For one thing, the targets of these drugs will be different. Genes themselves and the regulators of their expression will eventually come to the forefront of the new therapeutic arsenal. This is one reason for the excitement and effort that is being invested in the development of effective gene therapy strategies. Replacing a malfunctioning gene will cure, rather than treat, a disease. Alternatively, a cure might be found in delivering a functional copy of the disabled or missing protein. While simple in concept, both strategies face big obstacles—including getting the appropriate macromolecules to the cells and tissues where they will be effective.

Gene therapy research faces the challenge of designing effective delivery vectors and methods of integrating foreign genes into the genome. Similarly, protein-based therapeutics will also have to be delivered continuously unless other strategies are developed. In order for proteins to remain within their therapeutic indices—above the level at which they are ineffective, but below the level at which they poison—the proteins need to be administered in a controlled manner. Large, complex proteins, unlike peptides and other "small" molecules, must be delivered so that they are properly folded and not degraded during either packaging or delivery.

Several growth factors and cytokines with demonstrated abilities to induce cell proliferation and gene expression have been identified. Some, like IL-2, have found clinical use, and numerous others show clinical promise. Although small molecule mimetics that are able to take advantage of classical drug delivery methods will continue to be developed for some of these, it would clearly be an advantage to be able deliver the proteins themselves now, rather than wait for effective copies to find their way through development and clinical trials.

The promise of functional genomics will only be realized when the therapeutic genes and proteins that it helps identify can be successfully delivered. The review article article in this issue (p. 153) discusses approaches that are being developed to overcome the problems of protein stability during the design and subsequent therapeutic release of implantable devices. The research paper by Arras et al. (pp. 134, 159) describes the successful formulation of a "time-release" microparticle carrier to deliver fibroblast growth factor—with the potential to enhance angiogenesis—directly to the heart.

Rols et al. (pp. 135, 168) report the use of electroporation to potentiate the direct transfer of a gene and its encoded protein in the treatment of skin cancer. And Kuo and colleagues (pp. 136, 163) have created poly(ethylene-vinyl acetate) copolymer matrices that can be used, as in this instance, for the controlled release of antibodies. Although an implantable therapeutic reservoir has been described by Koole et al. (p. 172) for the slow release of smaller molecules, alterations in pore size may make this system amenable to the regulated release of protein therapeutics. Finally, a feature by John Patton (p. 141) discusses new developments in the mechanical delivery of therapeutics to the lung—an important "brute force" route for the delivery of macromolecules.

Despite the considerable difficulties that remain, the precise, local delivery of one or more therapeutics to a target or targets is en route to becoming a clinical and commercial reality. Drug discovery may be biotechnology's raison d'être, but its success is utterly dependent upon versatile delivery.

Biodiversity: Knowledge is power

When biotechnologists talk of exploring space, they are generally referring to the diversity space of protein and nucleic acid sequences—but just as importantly, there is the physical space that contains bioactive molecules. Accessing both kinds of space is both scientifically and commercially valuable, and presents investigators and entrepreneurs in countries previously on the trailing edge of biotechnology opportunities to join leading-edge biomolecular prospecting efforts as equitable partners.

Judging from the presentations and interactions at the *Nature Biotechnology*-cosponsored Second Monroe Wall Symposium on Natural Products Discovery, Biodiversity, and Biotechnology, translating these opportunities into viable plans and tangible products is gathering some momentum.

In parallel with the growing realization that the gems of bioprospecting include proteins for industrial, agricultural, and bioremediational purposes, is a growing appreciation of the value that accrues from having databases that relate sequence, metabolism, biology, and ecology. Unlike pharmaceutically driven bioprospecting, which uses screens to distinguish and purify lead compounds—and which has a potentially high payoff, but with lottery-like odds—these new complementary database approaches, aimed at directly accessing microbial (and plant) biochemical diversity, create knowledge bases that have commercial value whether or not a particular activity turns out to have the intended medical or industrial application.

Opportunities in developing countries to participate in these kinds of collaborations are not restricted to those with advanced biotechnology expertise and infrastructure. For example, even the least industrialized country is likely to possess unique plant and animal collections in its museums and university departments, the transfer of information about which to electronic formats would have value that could be leveraged significantly. It is this inherent conservancy rule of molecular diversity-based biotechnology that is one of its most appealing characteristics. Cultivation and curation of these "natural" knowledge resources by the countries of the South, along the lines of the databases being created by Mexico's National Commission on Biodiversity, or Costa Rica's INBio, would certainly help level the biodiversity playing field in ways that no treaty, standing committee, or stampeding herd of policy-riding diplomats ever could.