ASBC MEETING

MOLECULAR GENETICS AIDS NEUROBIOLOGY

PHILADELPHIA, Pa.—Along with virtually every other area of biology, the neurosciences are beginning to reap practical benefits from applying the techniques of molecular genetics. As Richard Goodman (Tufts-New England Medical Center, Boston, MA) demonstrated at this year's meeting of the American Society of Biological Chemists (ASBC), the ability to use cloned genes in transfection assays has already proved invaluable for defining neuropeptide-specific genetic regulatory sequences. And Paul Patterson (California Institute of Technology, Pasadena) revealed how the future cloning of the gene for a cholinergic differentiation protein could lead to improved treatments for neurological disorders like Alzheimer's disease.

The development of undifferentiated neural crest cells can be influenced in tissue culture by a number of soluble components—including nerve and epidermal growth factors, insulin, corticosteroids, and calcium ion influx. But noradrenergic cells also convert to fully functional cholinergic neurons during normal development *in vivo*. Using a variety of assays, Patterson purified a single protein capable of mediating this conversion. In conjunction with CalTech's Stephen Kent, he prepared synthetic peptides derived from the protein's N-terminal sequence and used these peptides to elicit antibodies. Such antibodies specifically inhibit the protein's activity; in fact, even the free peptide is an effective competitive inhibitor.

The researchers were therefore confident in using the peptide to design oligonucleotide probes in order to clone the gene for the cholinergic protein. Thus far they have picked out a number of cDNA clones—in a library from cultured rat heart cells—which hybridize at high stringency, although the team has not yet identified one that exactly matches the N-terminus of the cholinergic protein. Perhaps these probes will reveal a family of differentiation factors that might eventually be used to enhance the efficacy of transplantation regimes to treat degenerative neurological disorders.

Goodman and his colleagues have been studying the genetic regulation of another protein that profoundly affects the central nervous system: vasoactive intestinal peptide (VIP). This 28-amino acid hypothalamic peptide has a wide range of activities—from vasodilation, to regulating pituitary secretions, to serving as an excitatory neurotransmitter. Most of these activities can be explained in terms of VIP's ability to increase cyclic AMP levels. In turn, cyclic AMP positively regulates VIP gene transcription, apparently by activating a specific enhancer element.

Recently Goodman has delineated a 17-base sequence just upstream of the start of the VIP coding region, which is crucial for this cyclic AMP-dependent transcription. Site-directed mutagenesis of the enhancer-like element revealed an extreme specificity—a single base change near the middle was sufficient to abolish up to 75 percent of its activity. The scientists are now using this enhancer in attempts to purify the sequence-specific DNA-binding protein that mediates transcriptional control of this potent neuropeptide. **—Harvey Bialy**

RESEARCH PAPER ANALYSIS

TWO ADVANCES IN AGRICULTURAL BIOTECHNOLOGY

When genetic engineers discuss significant agricultural applications of their work, among the first advances mentioned are the anticipated production of transgenic crop species expressing insect resistance, and the generic manipulation of plant secondary metabolism. Two papers in this issue of *Bio/Technology* report important accomplishments in both these areas and illustrate the current rapid pace of development.

David Fischhoff and his colleagues at Monsanto (St. Louis, MO) describe the insect-resistance properties of a crop species engineered to express a bacterial insecticide gene: tomatoes producing the toxin from *Bacillus thuringiensis* (*Bt*) var. *kurstaki.* And Nam-Hai Chua et al., working at the Laboratory of Plant Molecular Biology at Rockefeller University (New York, NY), report a significant advance in our ability to engineer economically important plants with their description of an efficient transformation system for *Brassica napus*.

In California alone, the approximate cost (including material, machinery, labor, etc.) of spraying for lepidopteran pests of tomatoes is more than $8 million annually. But there is an important distinction between tomatoes grown for the fresh market and those for processing: Although the fresh-market tomatoes take up only about 10 percent of total acreage, intensive spraying expands the cost of pest control on these crops to some 30 percent of the total. In general, value added by rDNA will be higher for features that benefit the processor (or increase the value of the crop) than for characteristics that benefit the producer (by reducing cost). But it is very possible for *Bt*-based insect resistance to become a standard feature within a relatively few years by having boosted market share while no longer being priced at a premium.

Additional markets may be opened up with the kind of work reported from Rockefeller. The genus Brassica, in addition to the *B. napus* oilseed rape, includes important vegetable crops such as cabbage, cauliflower, broccoli, and brussels sprouts. Although markets for the products of oilseed rape are considerably larger than for vegetable representatives of this genus, the value of production of vegetables per acre (and generally per unit of seed) is considerably higher. This means that value added through genetic engineering will be significantly higher on a unit basis in vegetables, and that early accomplishments, such as the Chua work, will likely be applied in this area. New traits that might have significant value in vegetables include herbicide tolerance, insect resistance, and disease resistance. Other researchers—including those working to modify oilseed crops to produce vegetable oils with improved qualities, such as altered oleic acid content—will welcome the opportunity to apply recombinant DNA techniques.

As the barriers to genetic manipulation of economic crops are overcome, the issue of what new desirable traits to incorporate becomes more acute. For example, *Bt* toxin genes and *Bt* toxin have been used widely in agriculture for nearly half a century, but novel types of disease- or nematode-resistance based on new genes and new toxins will face daunting regulatory hurdles. **—David Wheat**

Dr. Wheat is a senior consultant specializing in biotech for Arthur D. Little (Cambridge, MA).