PLANT GENOME MAPPING

SERIAL RFLPS FOR CEREAL GRAINS

LONDON—Five European seed companies will help U.K. plant scientists complete restriction fragment length polymorphism (RFLP) maps of wheat and barley, Europe's two major cereal crops. In return, over the next three years the companies will gain sole access to new RFLP probes and the maps they generate.

The deal has been negotiated in the form of license agreements by Agricultural Genetics (Cambridge, U.K.), which is exercising its right of first refusal to exploit biotechnological research at the Agricultural and Food Research Council's Institute of Plant Science Research (IPSR) in Cambridge. A subsidiary of the company—Cambridge Plant Breeders (Cambridge, U.K.), which specializes in oilseed rape breeding—is one of the five licensees.

Another is Plant Breeding International Cambridge (Cambridge, U.K.), a subsidiary of the multinational Unilever (Rotterdam, Netherlands) built around the plant breeders who, until late in 1987, were colleagues of the laboratory-based IPSR scientists now producing the RFLP data. A third local licensee, Nickerson International Seed (Cambridge, U.K.), is a subsidiary of the petrochemical giant Shell (London).

Two major league players, ICI (Jealott's Hill, Berkshire, U.K.) and CIBA-Geigy (Basel, Switzerland) complete the quintet. Peter Innes, technology transfer manager of Agricultural Genetics, says many other companies in Europe—and some in the United States—were offered licenses, but seemed either unwilling to pay the substantial fee or not set up to use RFLP data in their current breeding programs.

According to Mike Gale, head of the Cereal Research Department at IPSR, the RFLP maps of both wheat and barley should be close to completion by the end of the three-year license period. "We are setting up a RFLP factory," he says, with the aim of producing a 10-centimorgan map of each plant. That will require about 25 RFLPs for each of the 21 chromosomes of wheat and seven chromosomes of barley. After completing the maps, any gene could safely be localized on a chromosome by its linkage to a RFLP, which will be no more than 20 megabases away.

Conventional mapping has already placed about 20 genes on each barley chromosome, but nearly all the genes are recessive, and of no use to the breeder, says Gale. Far fewer wheat genes are mapped at present, but those that are tend to be useful. To the five genes already mapped on wheat chromosome 7, the IPSR scientists have now added 18 RFLPs, which should greatly assist the mapping of additional genes.

Making RFLP maps of wheat and barley will progress in parallel, says Gale. Wheat arose only 10,000 years ago, and so there has been little outbreeding of the plant. Because it has three times as many chromosomes, and less of the variation in DNA sequence that enables RFLPs to be found, making RFLP wheat maps will be more difficult.

IPSR's stocks of wheat—each lacking one pair of the 21 chromosomes—and other stocks that carry single barley chromosomes will greatly aid the RFLP mapping process. "IPSR seems to be far ahead of anyone else in mapping cereals," says Mike Baylis of ICI. "We have bought a license to one of the most cost effective pieces of research in cereal breeding."

ICI, like the other licensees, will put the RFLPs to dual uses. One is to produce genetic "fingerprints" of their lines, both as a means of identification and to look for signs of exploitable genetic diversity among morphologically similar lines.

The other use is linkage. In some cases this will be simple, says Gale. A RFLP that distinguishes spring from winter types of barley, for example, already has been found and can be used to check seeds. Traits that are determined by many different genes present more problems, but eventually RFLPs may be used to screen seed for the presence of the different contributory genes. **—Peter Newmark**

MERGERS

R&D THE KEY TO DANISH CORPORATE COMBINATION

LONDON—A more natural merger than that planned for Nordisk Gentofte (Gentofte, Denmark) and Novo Industri (Bagsvaerd, Denmark), Denmark's two largest pharmaceutical companies, would be hard to imagine. Both are headquartered in the suburbs of Copenhagen, both have invested heavily in the biotechnological route to new pharmaceuticals, and, after Eli Lilly (Indianapolis. IN), they are the two largest producers and suppliers of insulin in the West. The combined entity—Novo-Nordisk A/S—may well supplant Lilly as the world's leading provider of insulin. But the cornerstone of this merger will be the two companies' combined R&D capabilities.

For Nordisk, the smaller and less well known of the two companies, insulin sales amounted to 77 percent of its $142 million turnover in financial year 1987–88, with human growth hormone accounting for most of the remainder. In the past few years, Nordisk has been busy switching to recombinant DNA technology for producing hormones and other pharmaceutical proteins. Its human growth hormone was the first recombinant product from Denmark, and the first to pass through the European Community procedure for high-technological medicinal products (see *Bio/Technology* **6:**1395, Dec. '88): it is now being produced at Nordisk's Gentofte fermentation plant.

Nordisk vice president for R&D, Søren Carlsen, is particularly proud of the technique that company researchers devised for making the authentic hormone: It is produced with a four-amino-acid extension in an *Escherichia coli* expression system, then the four amino acids are cleaved, a pair at a time, using an exopeptidase. The enzyme is inhibited from removing the next pair because one of them is proline (see *Bio/Technology* **5:**161, Feb. '87). Proline crops up in an appropriate position more frequently than one might expect, says Carlsen, citing the cytokines interleukins 1 and 2 as other examples.

Nordisk plans to produce recombinant factor VIII in mammalian cells, in a joint venture with Chiron (Emeryville, CA). This could fit nicely with Novo's production plans for a recombinant factor VIIa, Carlsen points out.

Better still is the fit between the expertise of the two companies in producing recombinant human insulin in yeast and in designing insulin analogs. Nordisk's plans to set up a production plant in Ireland, however, may well become redundant—Novo already has similar plans to produce insulin in Denmark, and has approval to market in several countries.

Both companies have cut their teeth in combining molecular model-