Interferon Congress Highlights

Cloning Results

Cloning of human interferon genes, which was but a gleam in researchers' eyes a mere 18 months ago (*Science*, 15 June 1979, p. 1183), is now rocketing ahead. The genes for leukocyte and fibroblast interferons have been cloned by several groups, some of which presented their recent results at the First Annual International Congress for Interferon Research.*

One of the more intriguing findings described at the meeting is the discovery that human cells contain several genes that code for leukocyte interferon. Using one of their cloned genes as a probe, Charles Weissmann and his colleagues at the University of Zurich identified ten such genes in the DNA from a single human fetus. A similar finding of multiple genes was reported by David Goeddel, Nowell Stebbing, and their colleagues at Genentech, Inc., and the Roche Institute for Molecular Biology. Human cells thus must have a minimum of five loci for leukocyte interferon genes—there can be two alternative gene forms at each locus—or they may have as many as ten loci. Both groups find that the nucleotide sequences of the individual genes differ from one another by about 15 percent.

This is the first of a series of brief meeting reports that will appear from time to time in Research News.

Not all of the apparent genes may be expressed, however. The Genentech workers, who determined the nucleotide sequences of eight of them, find that one contains stop signals that would prevent it from directing the synthesis of a complete interferon protein.

Another major finding of the sequence work is that the genes for leukocyte interferon lack introns, the segments of DNA located within most eukaryotic genes that do not code for protein structure. So far, the only other eukaryotic genes found to lack introns are those coding for histones, proteins thought to be involved in the control of gene expression.

The absence of introns has made life easier for investigators who want to construct bacterial "interferon factories" by putting human genes into bacterial cells. It means that they do not have to worry about whether the bacteria have the machinery to produce proteins coded for by genes with introns, which are not found in bacterial cells. In fact, the Genentech and Zurich researchers find that leukocyte interferon is made by bacteria if the genes are attached to appropriate bacterial control sequences before they are put into the cells. So far the bacteria carrying the human interferon genes are producing the agents in amounts of up to 200 to 250 micrograms per liter of bacterial suspension.

Moreover, the bacterial interferons are active. According to Weissmann, one of the interferons produced in this way displayed several of the agent's typical activities, including antiviral effects and stimulation of natural killer cells. Weissmann says, "This means that the multiplicity of genes is not needed to supply different interferon activities. One molecule seems to have them all."

Not only are the bacterial interferons active in laboratory tests, they also seem to work in the living animal. The Genentech group has evidence that bacterial interferon—a product of a human gene—can protect squirrel monkeys, mice, and hamsters against infection by encephalomyocarditis virus, which usually produces rapidly fatal disease in the animals.

If the bacterial interferons ever reach the stage of clinical testing in humans, however, there may be a complication. The bacterial products of the different leukocyte interferon genes are not equally active in eliciting antiviral activity in all cell types. As a result, they may have to be tested individually to determine their possible therapeutic efficacy.

Clinical Results

In contrast to the rapid pace of the cloning work, clinical trials of interferon are progressing more slowly, mainly because there is still so little of the agent to test. The results that are coming in suggest that while interferon is of modest therapeutic benefit to some patients with advanced cancer, it is not exactly a miracle drug, nor is it free of side effects.

Ernest Borden of the University of Wisconsin Medical School described the results of the initial phase of the American Cancer Society's (ACS) trial of interferon in patients with advanced breast cancer. The study included 26 patients treated at four medical centers (Wisconsin, Roswell Park Memorial Institute, Mount Sinai Hospital in New York, and M. D. Anderson Hospital and Tumor Institute).

Of the 26 patients, 6 achieved an "objective partial response" (defined as a 50 percent reduction in the sum of the products of the measurable diameters of the tumors), 5 improved somewhat, 8 remained stable, and 7 showed continued disease progression. As Borden assesses the results, "Interferon was no more active than other available single chemotherapeutic agents, and less active than available drug combinations." Nevertheless, he is encouraged to find that a protein of human origin can cause some disease regression and he thinks that it may have a role if used in conjunction with established drugs. Borden points out that the optimum dose schedule for interferon use remains to be established and that this will be a major goal of future studies, whether conducted by the ACS or other organizations.

Jordan Gutterman of M. D. Anderson described that institution's trials with interferon, which have been conducted mainly with patients who have breast cancer, multiple myeloma, or malignant lymphomas. (Most of these results were published in the *Annals of Internal Medicine*, September 1980, p. 399.) The M. D. Anderson results with breast cancer patients were generally comparable to those of the ACS trial; 7 of the 17 patients showed partial remission or some improvement. However, 2 of the 11 lymphoma patients and 1 of the 10 individuals with myeloma had complete remissions lasting for as much as 2 years.

All clinical trials with interferon have shown that it is not as free of side effects as was once hoped, and the clinical trials reported at the Interferon Congress were not exceptions. The most common side effects seen are loss of appetite, nausea, fever, hair loss, and depression of white blood cell counts.

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*Held in Washington, D.C., on 9 to 12 November; *organized* by Scherago Associates, New York, and the *Journal of Interferon Research*.

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