

Interferon was not the miracle cure for cancer hoped for in its early days

In the eighth article in a series on landmark drugs, Jenny Bryan looks at the early history of interferon. Although it failed to provide a cure for cancer, its success in other areas, such as multiple sclerosis and hepatitis, will feature in the next article in the series

When a “World in action” team turned up at the Wellcome research laboratories in Beckenham, Kent, in the late 1970s to make a programme about interferon, they made it clear they were after “the story, not the science”. The story — of a potential miracle cure for cancer — was making headlines around the world. But the science was a lot harder to interpret and, as it turned out over the subsequent 30 years, was not going to withstand the test of clinical trials or experience — at least in the field of cancer.

“Today, interferon only has a marginal role in cancer, in the treatment of malignant melanoma, renal cell cancer and some types of leukaemia and lymphoma. But in the late 1970s, we had high hopes for it,” explains Terry Priestman, consultant clinical oncologist at New Cross Hospital, Wolverhampton, who briefly left the NHS in 1977 to join Wellcome (now part of GlaxoSmithKline) as it attempted to develop interferon as an innovative cancer treatment.

“Until that time, interferon was in short supply because it had to be laboriously produced by extracting white cells from large amounts of donated blood, and stimulating them with virus particles to get them to make interferon. Wellcome developed a method of culturing huge quantities of lymphocytes in 20-foot high tanks and stimulating them to produce interferon, so I decided it was a good time to join the company and find out if interferon really was a realistic treatment for cancer,” Dr Priestman recalls.

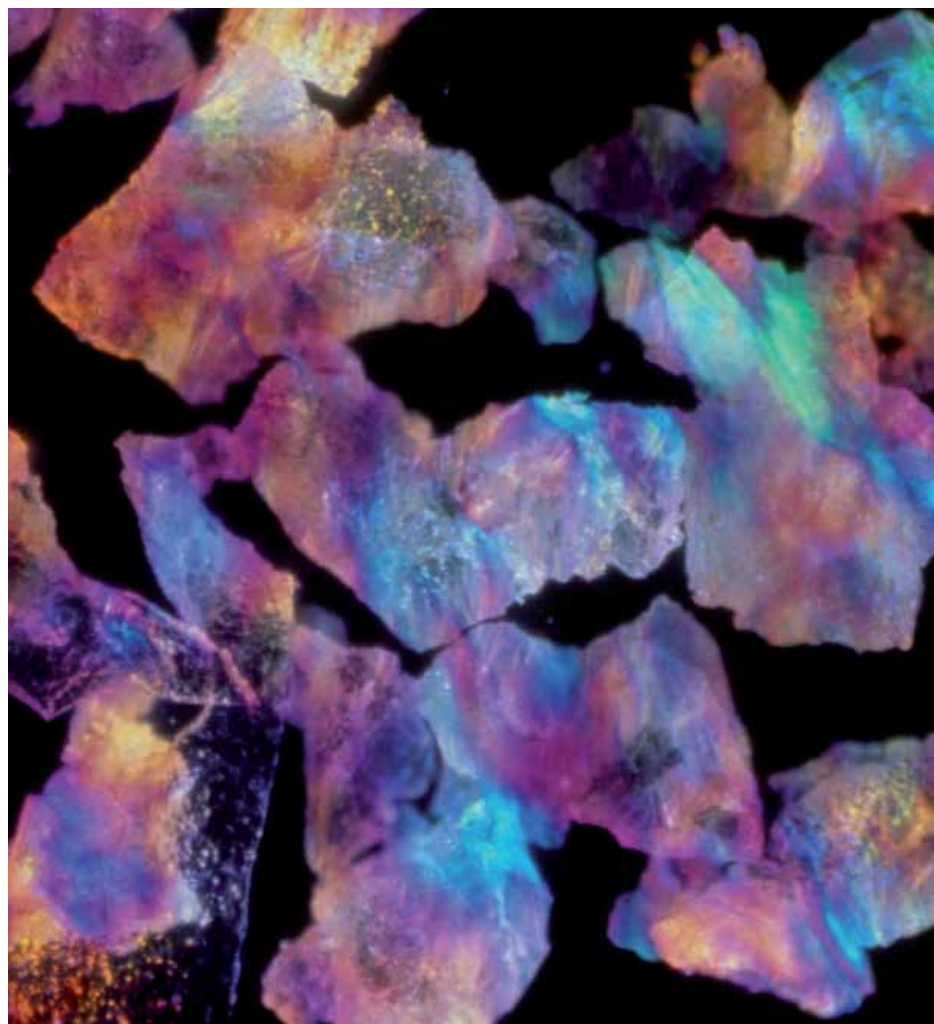
Long history

By 1977, interferon already had a 20-year history. In 1957, UK scientists Alick Isaacs and Jean Lindenmann found that a protein produced by embryonic chick cells, previously exposed to heat-inactivated influenza virus, could inhibit replication of live influenza virus.¹ The protein was christened interferon because it interfered with viral replication.

Initially, interferon was classified according to the type of cell it was made in — leucocytes, fibroblasts and lymphoblastoid cells.² But the different forms are now more usually called alpha, beta and gamma interferon.

During the 1960s, Finnish scientist Kari Cantell developed a way of extracting alpha interferon from leucocytes. But, worldwide, the substance remained in short supply, so that only handfuls of cancer patients could be treated, although seemingly with promising results.

At the Karolinska hospital in Sweden, twice as many patients with osteogenic sar-



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Interferon had to be produced by extracting white cells from large amounts of donated blood and stimulating them with virus particles

coma who were given interferon after surgery lived for three years than those who did not receive the drug.³ But the findings were based on fewer than 40 patients. Anecdotal reports suggested benefits in lymphomas and leukaemias and, in the US, researchers reported regression of secondary tumours and extended remission in women with advanced breast cancer.⁴

UK trials

In the UK, Wellcome pressed on with its new method of lymphoblastoid cell culture so that, in 1979, Dr Priestman was ready to begin phase 1 trials. The research programme nearly came to an abrupt end, however, when the first patient to be injected with the new form of interferon — a 19-year-old man with

advanced Hodgkin's disease — had a non-fatal acute respiratory arrest shortly after his injection.

Fortunately, the rather less serious flu-like symptoms, which have become interferon's trademark side effects, were the main adverse events recorded in the rest of the patients in the study.⁵ But, as Dr Priestman explains, even this was a surprise: “We had assumed that, as a natural biological product, interferon would not have side effects, and this was supported by preclinical studies. But, as experience gathered in clinical trials, we saw that there was significant toxicity, and it was suggested that it is actually natural interferon that causes the aches and pains and fever when people get flu.”

Phase 2 trials of Wellcome's interferon were carried out in conjunction with the

Imperial Cancer Research Fund (now Cancer Research UK). But, although responses were seen in a few patients, particularly those with renal cell cancer, the overwhelming picture was disappointing.

Genetically engineered interferon

Wellcome's cell culture technology was rapidly superseded by genetically engineered interferon alpha produced by biotechnology company Genentech in 1980. This was licensed to Hoffman La Roche in 1986, and initially marketed for the treatment of hairy cell leukaemia and AIDS-related Kaposi's sarcoma.

But genetically engineered interferon fared no better as a cancer cure than its forebears and the underlying basis for interferon as an anti-cancer agent, which stimulates the immune system to destroy cancer cells, was fundamentally flawed. "Interferon represented a completely new approach to treating cancer, as it was the first cytokine to be used in this way. But we probably should have been more sceptical and realised that trying to use the immune system to fight cancer would be a lot more complicated than that," Dr Priestman explains.

The discovery of other families of cytokines that could be used as immunomodulators in cancer treatment proved equally fruitless and, in the case of the interleukins, significantly more toxic than interferon.

"The demise of interferon was partly due to a long-term sense of disillusion in the immune system approach, but also to the arrival of a new generation of biological agents, such as the tyrosine kinase drugs and antiangiogenesis agents, which are much more exciting, and for which the underlying biological mechanisms are much better established," says Dr Priestman.

He highlights the more targeted approach of today's novel anti-cancer drugs, such as imatinib (Glivec) for chronic myeloid leukaemia and sorafenib (Nexavar) for renal cell tumours, which are displacing interferon from even the cancers where it ultimately found a niche role.

Almost the only cancer in which interferon still plays a significant role is advanced malignant melanoma, where recent studies suggest that adjuvant interferon alpha reduces relapse and prolongs survival, but with a rather limited absolute survival advantage of 3 per cent over five years.⁶

Further research has shown that a pegylated formulation of interferon alpha, designed to prolong the drug's activity and improve its effectiveness, prolongs relapse-free survival, especially in patients with least nodal involvement or with ulcerated disease. But no impact on overall survival has yet been seen.⁷

Despite the enormous hype of three decades ago, interferon leaves little legacy in cancer treatment other than to induce greater

realism in the appraisal of future cancer drugs, believes Dr Priestman.

"An interesting but blind alley" is how he sums up the story of interferon and cancer. Fortunately for the pharmaceutical companies that put so much time and money into developing the drug, the story has proved to be very different in other therapeutic areas, notably hepatitis and multiple sclerosis.

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