Recreating an Environment for Clinical Discovery

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Introduction

The purpose of the first annual Emil J Freireich symposium was to celebrate life, creativity, and stories of medical discovery. Many of the stories were about J Freireich’s own discoveries, and many were about the discoveries he inspired others to make. The importance of these narratives lies not only in the discoveries themselves, but also in what they reveal about the nonlinear manner by which medical advances occur. This paper illustrates the role that J Freireich played in stimulating the clinical development of IFN-α and, more broadly, in the early development of clinical cytokine research.

In April 1975, J called and told me about a meeting that Mathilda Krim had organized in New York on a substance called IFN. Dr. Lee Clark informed J of the meeting, but no one in Developmental Therapeutics could attend, and J himself could only go for one day. He asked if I would be willing to attend the meeting. Not knowing what was to lie ahead, but knowing J’s wonderful instincts, I said, without hesitation, “I’ll be there.” That meeting changed my life. At that conference, I discussed with Mary Lasker a potential financial commitment to study the clinical effects of IFN in cancer based on the work by Hans Strander and Kari Cantell. She considered money “frozen energy,” and eventually, with her resources, we unleashed a major study of the first biological growth inhibitor in the treatment of human malignancy.

Part I—1976–1986: From Technology to the Clinic

The environment that J had created in the Department of Developmental Therapeutics allowed me to exploit the revolutionary changes that were occurring in the biomedical sciences. Most people hesitate to go in uncharted directions; because of J’s leadership and encouragement, I was able to help develop a new field in which I otherwise might not have participated. Our interest in IFN had, in part, been stimulated by the clinical investigations by Strander and coworkers at the Karolinski Institute that suggested that partially purified IFN could delay recurrent growth of tumor in osteogenic sarcoma patients after surgery (reviewed in Ref. 1).

With the support of the Lasker Foundation, we finally obtained the partially pure leukocyte (now α) IFN and initiated clinical studies with a simple question: could a partially pure growth-inhibitory biological protein induce regression of metastatic cancer? As we published in 1980, the answer was affirmative (2). In 38 patients with metastatic breast cancer as well as refractory nodular lymphoma and multiple myeloma, IFN induced regression of tumors, thus demonstrating for the first time that a biological growth regulator could influence the survival of metastatic cancer cells. The results were a surprise to most medical oncologists and we met with great skepticism.

The skepticism, however, did not make things any less exciting. Scientists at the Roche Institute of Molecular Biology reported in 1978 on the first pure species of leukocyte IFN (3). In January of 1980, Charles Weissmann and colleagues, working with the support of Biogen, announced the first cloning of the leukocyte (α) IFN gene (reviewed in Ref. 4). This was soon followed by the cloning of IFN-α by collaborating scientists at Roche and Genentech. Within a year, we began clinical investigations with pure IFN-α2a with the scientists at Hoffman-LaRoche. Studies with the purified single-gene product confirmed the wide-ranging biological and clinical activity of the multispecies partially purified material with which we had previously been working (reviewed in Refs. 1 and 5). Many surprises occurred in our first study with the purified IFN. For one thing, we learned that the pyrogenicity that we had observed with the partially purified IFN was not due to contaminants but was in fact the property of the purified IFN molecule. Thus, we learned that the febrile response occurring during viral infections was due to a release of various endogenous mediators such as IFN. As we escalated to very high doses (about 0.5 mg), severe neurological toxicity manifested by fatigue and memory loss occurred. Over the next 2 years, laboratory and clinical studies with the recombinant molecule confirmed virtually all the biological activity that had been previously reported with the partially purified material (5, 6).

Fortunately, with private support from the IFN Foundation in Houston, we continued to study patients with the partially purified IFN as well as the recombinant IFN. With the former material, we showed modest biological and clinical activity in patients with slowly growing renal cell carcinoma (7). However, these results stimulated a new direction in our clinical program. At a developmental therapeutics clinical research conference in 1982, we discussed a patient with metastatic renal cell carcinoma treated with partially purified IFN-α who had achieved a complete remission. After the meeting, J walked down the hall with me and bellowed:

“Gutterman, what is the common denominator of those patients of yours and Quesada’s who respond to interferon?”

“Do you mean the slowly growing tumors?” I replied.

“Absolutely. Those that are well differentiated, those that are still capable of differentiating. Why don’t you work on CML and HCL?”

The abbreviations used are: CML, chronic myelogenous leukemia; HCL, hairy cell leukemia.
“Well, HCL would be easy since Jorge Quesada and Evan Hersh are very enthusiastic. CML will be more difficult because everybody I have talked to seems concerned that we will induce a blast crisis.”

With enthusiastic and passionate support, we studied both with surprising results. In 1982, no effective treatment existed for HCL, except for splenectomy. IFN-α turned out to be a remarkable substance. With treatment, we began to see restoration of normal hematopoiesis, initially in platelets and then in WBCs, neutrophils, and RBCs. Most of the infiltration in bone marrow was reduced. Eventually, cellular immune response was restored. The incidence of opportunistic infections dramatically disappeared, and requirement for blood cell support disappeared. The paper we published in 1984 in the New England Journal of Medicine changed the psychology on the use of IFN in oncology (8). It was quite clear that the empirical observation had a dramatic and lifesaving effect in many patients. This work was rapidly confirmed with the recombinant IFN (9).

At this point, the two pharmaceutical-biotechnology consortia developing IFN were then faced with a strategy to obtain United States Food and Drug Administration drug approval. I remember the argument at one of these companies. Part of the group insisted that we compare IFN to something else. “Why?” I asked. Trained in Freireich's principles, which were presented in his brilliant 1976 Karnofsky Lecture in Toronto (10), I explained: “We’ve already got the answer. We do not need to do a randomized study when the results are quite clear. It’s like when two statisticians meet on the street. One says to the other, ‘How is your wife?’ The other says, ‘Compared to whom?’ Either it is good or it is bad, and we know that IFN is good for people destined to succumb to advanced HCL.” Fortunately, both Hoffman-LaRoche and Schering-Plough elected to study a consecutive series of patients with the recombinant IFN. These studies eventually led to the approval in early June of 1986 by the United States Food and Drug Administration of IFN-2a and IFN-2b for the treatment of HCL.

Simultaneously, we began to study the effects of the partially purified leukocyte IFN in patients with CML in collaboration with the late Ken McCredie as well as with Moshe Talpaz, and later with Hagop Kantarjian (11). The initial paper published in 1983 (12) and confirmed with recombinant IFN in 1986 (13) demonstrated that in early CML, we could get selective suppression of leukemia cells bearing the Ph+ chromosome with restoration of the normal clone of cells. Patients with advanced blast crisis, in general, were refractory to the biological activities of IFN-α.

The lessons learned (see Ref. 6) in CML, I think, will have important applications in the further use of IFN in cancer. It seems that IFN can overcome the antipapoptotic effects of bcr-abl by presumably allowing for terminal differentiation and/or apoptosis of the CML cell. As the disease progresses with new cytogenetic and molecular abnormalities and the CML cell fails to differentiate, the effects of IFN become less and less apparent. Although the precise biological reasons for the effects of IFN have not been defined, it is clear that IFN can restore the adhesiveness of CML cells to stroma, probably by regulation of β-1 integrins (reviewed in Ref. 6).

It is still not totally appreciated by cancer researchers that IFN can achieve profound effects in cells still capable of undergoing differentiation. As tumors progress with multiple molecular abnormalities, the effects of IFN become insignificant. Thus earlier application of IFN, as has been done in primary melanoma (14), needs to be studied.

Part II—1986–1996: Biology Put in Place

During the next decade, we saw a wide expansion of clinical and biological understanding of IFN as well as other regulators of growth and differentiation. An early report in 1980 demonstrated that IFN-α could inhibit the motility of endothelial cells (15). Later reports showed that IFN-α could inhibit the process of angiogenesis in vivo, which then evolved as an important target in anticancer therapy. One of the earliest pieces of evidence that IFN could induce remissions in angiogenic diseases occurred with the treatment of Kaposi's sarcoma (reviewed in Ref. 1). IFN was approved in this country for the treatment of that disease in 1987. Soon thereafter, Folkman and coworkers demonstrated lifesaving effects in patients with fatal childhood hemangiomas (16). With the emergence and discovery of new potent antiangiogenic proteins (17) as well as small molecules, the introduction of IFN in combination with these agents will be quite exciting.

Today, IFN is applied in at least 16 disorders and is one of the largest-selling recombinant DNA-derived proteins (6, 18, 19). With IFN now as the prototypic cytokine, these substances have taken their place with other soluble, intercellular signaling molecules, including neurotransmitters, endocrine hormones, and autockoids (20). IFN, like these other extracellular signaling molecules, induces profound effects in gene expression, cytoskeletal architecture, cell-cell interaction, cell migration, and cellular metabolism (6). Recently, I proposed that the activity of IFN in malignancy, viral disease, angiogenic diseases, and fibrotic and inflammatory diseases suggests a spectrum of interrelated pathophysiology. In that review, I emphasized that the targets for IFN-α now include extracellular matrix and tumor stroma, cell adhesion molecules, cytoskeletal function, signal transduction pathways, and cell cycle control (6).

Table 1 lists some of the lessons learned in the clinical development of IFN. In the environment created by J Freireich, we were taught to expect the unexpected. Our ideas were always given free rein as long as they made sense and followed proper clinical investigation. Many of the advances that were surprising have nourished basic research studies in the laboratory, particularly from our clinical studies in CML and HCL. Finally, the history of drug development has proven time and again that many important observations are made after regulatory approval. This is certainly true for IFN. As its use has expanded, new insights have been revealed (6, 21). This is why Dr. Freireich's urging for earlier approval for drugs, particularly in oncology, is so appropriate.
Part III—The Future: Genomics and the Clinical Application in Cancer Research

Starting today and looking as far as we can into the future, genomics will revolutionize our understanding of human biology, physiology, and therapeutics (22). We will be able to dissect genetic circuits and make advances that were unimaginined in 1976, when the studies with IFN were conceptualized. These advances will be as unimaginable for us today as the cure for childhood leukemia was for J when he was a boy.

Until 5 years ago, we studied individual genes and proteins. The 21st century will be an era of biological complexity. Today we are accumulating, through genomics, massive amounts of data that are being formulated into information. Eventually, this information will be transformed into profound knowledge of genetic circuits. Physiology and pathophysiology of the human organism will undergo unanticipated new definitions.

At M. D. Anderson Cancer Center, we are beginning to make a major effort in the genomics area in celleratation with genomics groups. Powerful new tools of DNA sequencing, transcriptional profiling, and application of mass spectrometry will redefine and reclassify tumors. Thus, genomic analysis of tumors will give us a power of understanding greater than that achieved with the microscope. For example, with the use of DNA microarrays and silicon chips, we will be able to probe normal and tumor tissue for the differential expression of thousands of genes (22, 23). Genomics will uncover many new genes and explain therapeutic resistance, propensity to metasta-size, and so forth. Powerful new diagnostic tests will be developed from body fluids with mass spectrometry. Eventually, the common malignancies will be redefined into 6–10 subtypes. This information will lead to more precise decision making regarding prognosis and treatment. Hence, oncologists of the future will use bioinformatics to help guide therapeutic decisions.

Our experience with IFN in HCL can give us a glimpse of the application of genomics. Because we had tumor markers to define HCL as a disease distinct from other B-cell disorders, we were able to quickly recognize the important activity of IFN. In the future, subclassification of all tumors by genomics should lead to similar recognition of therapeutic success in defined subclass groups.

What will this mean for drugs in the near future? In the first 50 years of drug discovery, most of the targets that bound small molecules were in three or four classes, including G-coupled proteins, enzymes, ion channels, and hormones (24). But the powerful new technologies, including combinatorial chemistry and high throughput robotics as well as bioinformatics, will revolutionize drug discovery. The targets for the 21st century will also include complex macromolecular interactions, including those that occur between proteins, between proteins and DNA, and between proteins and RNA.

The era of genomics is an era of great opportunity as well as discontinuity. What concerns me greatly is that we have become numbed and desensitized to the insidious rules and regulations of managed care and regulatory agencies. In a recent paper, the group from Stanford has described the critical importance of the academic clinical scientist in driving the process of pharmaceutical innovation (25). Recently, I emphasized that the public sector and the private for-profit sector must learn to work together in an evolution of cooperation if we are to deal with the massive body of new scientific data and begin to transform it into a clinical reality (21). Physician scientists of the future must not be translational scientists but must in fact act more as a ribozyme; that is, they must act as catalysts. By doing so, we can begin to recreate the environment for clinical discovery in the 21st century that J Freireich created at M. D. Anderson Cancer Center.

J Freireich’s career has touched the lives of thousands of clinical and basic researchers. All of us should be inspired to carry out the passionate principles Freireich has proposed. The Talmud says when you’ve saved a single life, you have saved the entire world. J Freireich has saved many worlds.

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References


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