

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## Rethinking the Randomized Clinical Trial: the 21<sup>st</sup> Century Application of Freireich's Laws

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### H&O What prompted you to create Freireich's laws?

**EF** In 1976, 28 years after randomized trials were invented, I was alarmed because I began to see in the literature clinical trials where the objectives of the study were allowing physicians to participate in trials where the patient didn't come first. Granted, the dividing line between experimenting and doing research was not very well defined at the time. By then, I had over 20 years of experience in treating cancer; and as my colleagues and I succeeded in curing children with leukemias, Hodgkin's disease, and lymphomas, we began to realize that the randomized trial technique was very useful, although it could be easily abused.

This same year I was asked by the American Society of Clinical Oncology (ASCO) program committee to give the 7th annual Karnofsky lecture. The previous 6 people who got this prize were unspeakable giants in oncology, and I knew this could not be an ordinary scientific lecture. So I decided to say something that would guide investigators to clearly discriminate between treating patients and treating experimental animals, and this is why my lecture was called "Mouse vs man." As I thought about these problems one at a time, I realized that I could formulate a simple statement that would remind people to perform correctly as physicians—that is why I created Freireich's laws.

My lecture covered 7 areas, and for each of those areas I formulated a law. These laws applied to research in people, limited neither to sarcoma nor to cancer in general.

### H&O Which law or laws do you think are most important to apply in the treatment of cancer patients today?

**EF** Law #3: if you need to experiment on people in order to gain knowledge, then its better to do without that knowledge. That is the fundamental principal that I was driving at. There are some things in science that you just don't need to know. The same principal applies to cancer treatment today. I presented these laws in 1976. Now, 32 years later, I still see publications in the literature where clinical trials are experimenting on people.

This relates to another very important law, law #1, which says that the primary beneficiary of clinical research is the patient participating in that research. Clinical trials are still being performed in which the control group is getting treatment that the investigators know is going to be inferior. This is done in order to objectively and scientifically establish that what they think is true is in fact true. When I finished the Karnofsky lecture, I did not publish it. I received tremendous feedback because the lecture was very controversial, and I was dependent

on research grants and peer reviews for my manuscripts. The lecture was finally published in 1997 on my 70th birthday, 21 years after I had presented it.

**H&O** One of your laws says, “Don't let toxicity interfere with success.” How do you respond to clinicians who say it is better to palliate terminally ill patients instead of treating them?

**EF** There is a great tendency nowadays to offer patients palliative care because of the concept that at some point, people are hopeless and they should give up treatment. Well, I feel very strongly that when you abandon hope, that is the cruelest torture that you can expose a sick patient to. Fortunately, we live in a community and a culture where no patient has to abandon hope. In my opinion, patients who think they have come to an end need to get on the internet and see what kind of treatment is available for them. This is Freireich's law #2—be prepared for success. What if the new drug ends up curing cancer? I have seen this in my life as an oncologist. The main point is that doctors need to be prepared for success because patients want success. From my experience, patients don't like being told that it is hopeless—they like to have some optimism.

**H&O** What role do you think the US Food and Drug Administration (FDA) should play in the regulation of cancer treatments?

**EF** I think it is unfortunate that in an effort to protect healthy people from unsafe drugs, we are applying the same rules to desperately ill people who are without hope. Presently, the time it takes from creating a new drug to bringing it to the market is approximately 15 years; 60% of that time is spent getting an investigational new drug application (IND) and satisfying regulators, claiming that you have killed enough animals and that the drug is safe enough to be given to humans. Because we now have sophisticated ways to do clinical trials, we can safely study drugs in humans without doing unnecessary animal testing. We can start to use drugs based on their pharmacology, biology, and biochemistry. It costs millions of dollars to get a drug through the IND phase and, in my opinion, regulation is a tragic problem. For this reason, I created law #7, which deals with regulation; the law says that a general solution to a specific problem will soon become a specific problem requiring a general solution.

What is problematic is that once an IND is obtained, testing is permitted in humans, and a phase I trial determines a drug to be effective, it still has to proceed to a phase II trial. This is an example of doing clinical trials when you already know the answer. Currently, when a

drug completes phase I and is found to be active, not only do patients have to participate in a clinical trial where they have a 50/50 chance of getting the drug, but if they are not eligible for the trial they cannot get the drug at all. No one benefits from that.

Unfortunately, the public isn't afraid of cancer so they are not as politically active. If a drug is delayed for 10 years, 6 million people will die of cancer. There is no reason to have an IND, which slows accessibility of cancer treatments. The government should not interfere with research and they should not regulate the IND. If an establishment like M.D. Anderson—which has peer reviews and grant reviews—has a proposal, they should be able to go ahead with their study without the interference of the FDA. *You have to be prepared for success.* There is no reason to do randomized trials with a drug that looks very promising.

If I have an idea to do testing in man, my proposal has to go through my department of specialists in the field, then it proceeds to the division level where numerous physicians review the protocol to be sure it is likely to succeed, sane, rational, and scientifically valid. Then it has to go to a research committee, which is composed of all the segments in the institution, including pharmacy, statistics, mathematics, and chemistry. They are all represented on a committee that looks at every protocol to ensure that the science is safe. After that, it is sent to the Institutional Review Board (IRB); the IRB has to determine whether this proposed clinical trial is ethical, rational, and justifiable in man. So where does the federal government come in? If someone is dying of cancer, that is not the FDA's business, it is the academic medical community's business.

If you study a drug quantitatively and objectively, you give it to people with a given disease at a given stage and they respond objectively with either regression of tumor or prolongation of survival. What is the necessity of controls if people are living? The fact of the matter is that a randomized trial can be conducted in which the objective has nothing to do with controls.

Randomized trials give you results for the average patient, but there is no average patient because everyone is different. Therefore, if a trial is performed in 1,000 patients and treatment A is better than treatment B, it does not necessarily mean that all patients should receive treatment A. As an example, there is a very rare form of acute myeloblastic leukemia that occurs in 10% of patients: acute promyelocytic leukemia. This disease is cured from a combination of all-trans retinoic acid and arsenic trioxide. This combination doesn't work for any other kind of acute myeloblastic leukemia or any other type of leukemia, but if a randomized trial of this combination therapy compared to another treatment is

performed, it would fail because it only benefits 10% of patients. The main focus now is on personalized medicine. Instead of trying to find out if treatment A is better than treatment B for everybody, the question is who benefits from treatment A and who benefits from treatment B. Therapy is based on the characteristics of the specific patient. So the big clinical trial thing, that era is over. Individualized personalized therapy is the new approach to treatment.

### H&O What is the future of individualized therapy?

**EF** Firstly, we have to understand the disease. When someone is infected with an organism, the organism is isolated, tested against an antibiotic, and then the patient is treated with the antibiotic that kills that organism. This is going to be the process for cancer. We find out what kind of cancer the patient has, what is wrong with their genes and with gene regulation, and we devise a drug that will work specifically for that. This is what occurred in chronic myelogenous leukemia where we found that the *BCR-ABL* gene was the driver. A drug was created that inhibited the proliferation of the *BCR-ABL* gene and the disease receded. However, this did not work for any other disease—only for those patients who had that particular genetic constitution.

So, increasingly we are going to turn to pharmacogenomics. Every person handles drugs differently; some patients take a drug, catabolize it immediately and it doesn't work. Other patients don't catabolize it and it works tremendously.

We also need to know the genomics of the tumor. We not only need to know how the patient's genetic makeup handles the drugs, but also how the cancer cells will respond to the drugs. This is true of all cancers if we can find a genetic basis for the cancer survival. We now have the tools to do X-ray crystallography to visualize the secondary structure of the drug. We know the atomic structure, and we have a library of every small molecule that can be made.

Thus, investigators need to put their understanding of the genetic basis for the cancer together with a search for drugs that can influence it favorably. We don't give insulin to normal people, we give it to diabetics because they don't produce it or don't produce enough, just like we don't administer antihypertensives to people with normal blood pressure, only to those with hypertension. The same applies to cancer. We are going to treat cancers not based on average outcomes in big clinical trials, but based on understanding the disease and devising treatment specific to that person's disease. I am a very strong supporter of individualized

#### Freireich's Laws

**Law #1:** The primary beneficiary of clinical research is the patient participating in that research.

**Law #2:** Always be prepared for success. Failure creates few problems.

**Law #3:** If we must experiment on patients to obtain medical information, then we had best do without that information.

**Law #4:** The best therapeutic research gives the best results.

**Law #5:** "Primum Non" fail to do the possible and the necessary.

**Law #6:** The best patient care (service) is clinical research/the best clinical research offers the patient the best possible care.

**Law #7:** The general solution to a specific problem will soon become a specific problem requiring a general solution.

Adapted from Freireich EJ. *Clin Cancer Res.* 1997;3:2711-2722.

therapy. We will cure cancer by understanding it, not by doing large randomized studies.

### H&O Why are you a supporter of the Abigail Alliance, which seeks to pass legislation to amend the IND process?

**EF** The Abigail Alliance is an advocacy group that is pushing for regulatory changes in the FDA that would allow patients with cancer and other life-threatening illnesses who have exhausted all other treatment options to have access to investigational drugs after phase I testing. When I became a supporter of the Abigail Alliance, ASCO opposed it. They wanted to "protect the clinical trial enterprise." Some of the arguments that were made against the Abigail Alliance were: 1) no one knows if the drug is really safe, as it only completed phase I; 2) it will destroy the clinical trial process; 3) the drug industry is going to profit.

Although it may be true that no one knows the exact side-effect profile of investigational drugs in phase I testing, phase II trials are still conducted in patients regardless. Also, providing access to investigational drugs will not destroy the clinical trial process because it is confined to patients who cannot participate in clinical trials. Finally, the drug industry will not be profiting from the access of unapproved drugs because pharmaceutical companies are required to provide the drug at cost as long as it is

not FDA approved. The bottom line is that there is no rational argument against the Abigail Alliance and their mission. Once a drug completes phase I, it should be the decision of the patient and their physician of whether or not that drug is right for them.

The legislation that the Abigail Alliance is seeking to pass is The Access, Compassion, Care, and Ethics for Seriously Ill Patients (ACCESS) Act. If passed, this bill will increase patient access to treatments in the investigational phase of FDA approval and would create an approval system for drugs, biological products, and medical devices that are responsive to the needs of terminally ill patients.

Senator Sam Brownback of Kansas introduced this legislation into the Senate in May 2008 and it is cosponsored by Senators Bob Casey, Jim Inhofe, Arlen Specter, and Norm Coleman; congresswoman Diane Watson introduced it to the House.

I think in order for this to be successful we have to arouse the public. When the public realizes that regulation is preventing them from getting the treatment they would need if they were diagnosed with cancer, they will influence their legislators.

I am in the position of facing patients every day who want progress and hope. The only hope for accelerating the development of treatment for cancer and other serious and life-threatening diseases is legislation, and that is why I am such a strong supporter of the Abigail Alliance and this legislation.

## H&O What advances do you hope to see in cancer research in the future?

**EF** We are beginning to understand the molecular basis for cancer. We know what the disease is and we have the tools to devise treatments. In the next decade we are going to utilize this knowledge to create patient-specific therapy. Today, 50 years after I completed my medical training, 100% of patients can benefit from cancer treatment. They aren't all cured—the cure rate may be 20% or 30%—but things are changing very rapidly. So in the next 50 years I think cancer will be like diabetes or hypertension. We will never be able to eliminate cancer, but will learn to manage it. It will be a chronic disease. We can control the proliferation of the cancer, maintain normal organ function, and transplant and replace organs. Also, I think in the next 50 years we will see an explosion in life expectancy, partly due to the management of this disease.

## Suggested Readings

Freireich, EJ. Who took the clinical out of clinical research?—mouse vs man: Seventh David A. Karnofsky Lecture-1976. *Clin Cancer Res.* 1997;3:2711-2722.

Freireich EJ, Kurzrock R. The role of investigational therapy in management of patients with advanced metastatic malignancy. *J Clin Oncol.* 2008 [Epub ahead of print].

Freireich EJ. The investigational new drug application—who benefits? *Nat Clin Pract Oncol.* 2006;3:62-63.