Towards a Unifying Theory of Clinical Research

WHERE IS OUR BIG BANG?

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Recently, a trainee came to me to discuss a proposed research project: “What I have decided to do is genetic profiling of all subjects about to receive investigational cancer chemotherapy at our institution,” he said. “I would like to compare genetic profiles with treatment outcomes, so I can begin to determine prospectively who’s going to respond to treatment or not, based on genetic markers.... Ultimately, I want to develop a unified theory that predicts which anticancer drugs are likely to be effective in which patients.”

What did I do? First, I tried to encourage this student, while pointing out the pitfalls inherent in such a broadly based experimental design; note that I did not use the word “unfocused.” What intrigued me most about this encounter was the concept of a “unified theory.” There are few unifying theories in biology—evolution of biological systems being one that comes to mind. The possibility that there might be more unified theories in biomedicine waiting to be uncovered is quite exciting.

One of my mentors and heroes, the late Lewis Sheiner, MD, who was professor of medicine at the University of California, San Francisco, and one of the fathers of population modeling of pharmacokinetic data, once told me that if medicine could make itself more like physics and less like biology, progress would come more rapidly. I used to think Dr. Sheiner’s axiom was correct, and his comments may yet prove prescient. But as someone who gravitated away from computers and mathematical models, and toward patients and clinics, the concept of clinical physics and unifying theories became more distant to me. Why?

My area of scientific endeavor has been early-phase drug development for HIV/AIDS. At Johns Hopkins, I teach the university’s only course on drug development. I begin this course by telling my students that each time a new molecule succeeds in making it from the laboratory to the drugstore, there have been, on average, 9 that have failed after entering clinical testing. Molecules drop out for a variety of reasons, but this 90% failure rate is axiomatic, and has not changed in the last 50 years. One possible explanation is that we have been unable to identify unifying theories about drug development that would allow us to improve our success rate. Another possibility is that clinical drug failures result from factors that are largely beyond our control, including the inherent unpredictability of human biology. If the latter is true, we can expect a high failure rate in clinical drug development for some time to come, despite the improving quality of our science.

I have long been interested in factors that contribute to intersubject and intrasubject variability observed in responses to anti-HIV drugs. We once performed a study in which we got 10 compliant HIV-infected patients who had fully suppressed

their plasma HIV RNA to undetectable levels for more than 3 months to return to clinic every Monday, Wednesday, and Friday for several months so we could measure their antiretroviral drug concentrations. To our great surprise, plasma concentrations of these drugs varied widely from visit to visit in most subjects, even though all reported strict adherence to the prescribed regimens.¹

The science of pharmacology would have predicted that drug concentrations in these exemplary patients would vary little from day to day, but the opposite was observed. There are many possible explanations for this result, some related to artifact and analytical variability, but most related to the biology of human subjects. Human behavior is complex and unpredictable. We vary greatly in what we eat and when we eat, what other medications and health supplements we choose to take, and what information we choose to disclose to our healthcare providers. These are the kinds of things that muddle the interpretation of our experiments. This is also a good example of the scientific complexities that must be embraced by our trainees in CTS research. I will also point out, gratuitously, that these are complexities rarely faced by bench scientists.

The unexpected can and will happen during clinical research. In fact, this is one reason I find clinical drug development to be so interesting. Patients who take investigational drugs frequently develop adverse reactions that were not anticipated by cell culture or animal studies. Our pharmacopeia is full of effective agents that were originally developed for one condition, only to veer off in a completely different therapeutic direction because of a chance clinical observation or “toxicity.” Sulfonylurea oral hypoglycemics and cGMP-specific phosphodiesterase type 5 antagonists for the treatment of erectile dysfunction are but 2 examples out of many.

My personal experience with this kind of serendipity involved studies of a first-in-class antagonist of the CXCR4 chemokine receptor that was developed as a possible anti-HIV drug. This agent turned out to have disappointing antiviral activity in HIV-infected patients, but it was terrific at stimulating increases in circulating neutrophils, monocytes, and lymphocytes, even in healthy volunteers. This chance observation—the result of noticing unexpected increases in peripheral leukocyte counts—led to the eventual approval of this drug, *plerixafor*, as an adjunctive treatment for stem cell mobilization after cancer chemotherapy.² Chance observation and variability in drug response can lead to scientific insight. But it often stands in the way of our attempts to make generalized conclusions, especially when studying small numbers of subjects. Our attempts to homogenize and control study populations encounter not just practical impediments but ethical ones as well.

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