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Translational Medicine: Proceed at Your Own Risk

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Abstract

Although investigators are encouraged to translate their laboratory research to impact the care of patients, there is an unappreciated downside to participating in “T1 translation” from the standpoint of the investigator if their translational efforts do not yield positive results in pivotal clinical trials.

One of the goals of the NIH Roadmap initiative was to facilitate the translation of research findings from the laboratory into clinical trials (T1 research)[1]. Although the recent focus on translational research in academia is laudable and is undoubtedly in the best interest of society, this new direction does expose investigators to certain personal and professional risks that can negatively impact their careers. This commentary, which is written from the perspective of two academic investigators who have experienced the “other side” of T1 translation and yet continue to engage in translational research, is intended to help investigators become aware of the limitations of clinical trials, as well as provide guidance to investigators who choose to engage in translational research.

Clinical Trials Often Fail for Reasons that are Unrelated to the Scientific Hypothesis Being Tested

Although randomized clinical trials represent the state-of-the-art approach to demonstrating the utility of a new drug, all that one can take away from a positive or negative clinical trial is whether a given drug is effective in a selected patient population. Unfortunately, a negative or neutral clinical trial result is often interpreted as proof that the mechanism of action that formed the basis for the trial is incorrect. Although that is certainly true in some instances, what is less well appreciated is that clinical trials usually do not provide precise information on disease mechanisms or on the mechanisms of action of a given therapeutic agent. Since most drugs exert pleiotropic effects, and since many drugs have off-target effects that can offset their potential benefits, it is not always possible to infer mechanisms of disease from trial results. Thus, negative trial results do not always indicate that the

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hypothesis supporting the drug use is incorrect. Indeed, many early clinical trials get it wrong in the first instance; for example the early use of beta-blockers in patients with heart failure was attended by worsening heart failure[2]. Although beta-blockers are a main stay of therapy for virtually all patients with heart failure today, it took years for investigators to find the right dose of the right beta-blocker, the proper timing to initiate therapy and the right patient population. Unfortunately, we have learned to worship at the fount of evidence-based randomized clinical trials, without understanding what is actually being reflected by the results of these trials. There are additional reasons why clinical trials fail that have little or nothing to do with the hypothesis that is being tested. The selection of patients for entry into clinical trials is not necessarily driven by scientific understanding of the appropriate patient population. Trial design can be affected by market forces; a broader label for drug use may be a must for pharmaceutical companies to invest in developing the drug. Slow enrollment of patients into a trial may also drive inclusion of larger patient population than the one expected to benefit most from the treatment. By including a broader patient population, the benefit of the drug may be muted, and the overall results of the trial may be interpreted as negative, even though the drug may have worked in the appropriate subgroups. Choosing the wrong dose/dosage of the investigational drug is another common problem. Indeed, the translation of a drug dose from animal to human studies is not always clear because of unanticipated drug/food interactions, drug metabolism, or other unanticipated variables that can mitigate the potential benefit of a new agent. Finally, advances in the field and improvement in patient care can reduce the statistical impact of the tested treatment. For example, mortality from myocardial infarction declined from 10% to 3% from 2000 to 2008, which means that an investigational agent to treat myocardial infarction would require a much larger sample size to show a significant benefit[3].

The Impact of Translational Research on the Investigator

Investigators are under increased pressure from funding agencies to engage in research that is clinically relevant. Indeed, researchers are asked to indicate the significance of their findings with respect to human disease, and/or to engage in pilot translational studies that demonstrate the utility of their laboratory bench findings for patients. The last line of research grant proposals is frequently a statement that if the hypothesis is confirmed the results may alter clinical practice and provide new treatment. Moreover, most investigators believe that it is part of their contract with society to engage in research that will benefit humanity. Viewed together these points suggest that there is increasing pressure on investigators to engage in T1 translational research. However, despite the societal importance of engaging in translational research, there is a downside to engaging in translational research that is rarely discussed.

For investigators who engage in T1 research, the failure of a pivotal trial that began in their laboratory to reach its primary endpoint is difficult personally and emotionally, especially if there is a suggestion that patients were harmed. Second, there is often the impression that because a clinical trial is negative their entire field of endeavor is “dead,” and that their line of research is without merit. This can have an obvious negative impact on the investigator for future publications and funding. Given how little clinical trials actually tell us about disease mechanisms and how often clinical trials fail[4], this judgment by the academic

community is unfortunate and can impede new ideas from being developed at time when new therapies are desperately needed. Moreover, when a clinical trial is “negative” there is often little interest and great delays in publishing the negative results and crucial elements of the study are often not reported. Finally, many investigators may be bound by confidentiality agreements, and therefore are not at liberty to address the criticisms of their peers.

How Can Investigators Who Engage in T1 Research Safeguard Themselves from These Problems?

The development of new drugs is an extremely long process that absorbs a substantial proportion of an investigators professional career. Investigators who choose to follow this pathway should understand that the likelihood of success in a phase III trial is astonishingly low in some clinical areas[4]. This statement should not be interpreted as suggesting that investigators who would like to engage in T1 research should abandon their research efforts or translational aspirations; rather they should stay focused on the biology that formed the basis for their original hypothesis. The development of beta-blockers for the treatment of heart failure is an inspiring example of how investigators followed the data, and were not deterred by the initial discouraging results in clinical trials. Sildenafil was approved for pulmonary arterial hypertension and erectile dysfunction, yet it initially failed in phase II hypertension and angina pectoris trials[5]. Second, translational investigators should familiarize themselves with the basic principles of clinical trial design so that as their ideas are moved into the clinic, they can have input into the design of phase II trials that provide the “go/no go” signals for developing pivotal clinical trials. The high rate of failure in pivotal phase III clinical trials can be often traced back to problems with phase II trial design, wherein input from the investigator may be critical. Thus, it is important for those who engage in T1 translational research to stay involved with their research ideas as they move into the clinic. Third, the research community should insist on the timely and full publication of both negative and positive clinical trials, and delay judgment until it becomes clear why the trial is negative. Although none of these suggestions will ever completely protect investigators from the inevitable disappointment when their ideas are not borne out in pivotal clinical trials, we hope that a clearer appreciation of the risks and benefits of engaging in this exciting type of research will encourage investigators to continue with the important mission of translational research.

Reference List

1. About the NIH Roadmap. 2013. http://commonfund.nih.gov/aboutroadmap.aspx
2. Talwar KK. Hemodynamic predictors of early intolerance and long-term effects of propranolol in dilated cardiomyopathy. J Cardiac Failure. 1996; 2:273–277.
3. Mochly-Rosen D, Grimes KV. Myocardial salvage in acute myocardial infarction–challenges in clinical translation. J Mol Cell Cardiol. 2011; 51:451–453. [PubMed: 21851825]
4. Dimasi JA, Feldman L, Seckler A, Wilson A. Trends in risks associated with new drug development successr ates for investigational drugs. Clin Pharmacol & Therap. 2010; 87:272–277. [PubMed: 20130567]
5. Ghofrani HA, Osterloh IH, Grimminger F. Sildenafil from angina to erectile dysfunction to pulmonary hypertension and beyond. Nat Rev Drug Discov. 2006; 5:689–702. [PubMed: 16883306]