Patients suffering from cancer, as well as physicians and researchers, are always searching for positive clinical trial results. We all hope for the following success story: the molecule was discovered in the lab, animal studies showed dramatic tumor shrinkage, the phase I results looked promising, and the follow-up clinical trials led to regulatory agency approval—the bench-to-bedside breakthrough. However, in reality, only a minority of drugs entering phase I clinical testing will reach the market, with close to 30% and 60% failing at phase II and III, respectively. An added challenge involves the limited reproducibility of many preclinical results. The Reproducibility Project: Cancer Biology attempted to repeat experiments from 23 high-impact papers published about 10 years prior and found that fewer than half yielded similar results, with vague protocols and authors unwilling to provide details of preclinical work being prime limiting factors. Yet, in spite of the fact that the studies in humans are ultimately far more important to treating patients than preclinical studies, cell culture and mouse studies often land in high-impact journals, whereas the negative clinical studies that follow are often nowhere to be found in the literature or are published in obscure journals that are willing to accept negative results. Moreover, the results may be seques- tered from patients behind paywalls even if published. Furthermore, although positive clinical trial results are ushered in with great fanfare at professional meetings, a negative trial will often not see the light of day at such a meeting.

Outcome information from clinical trials is critical for physicians to provide the best care possible to patients. However, there is often a lack of enthusiasm from investigators and sponsors to submit negative studies and from high-impact journals to accept these publications. The Food and Drug Administration Amendments Act of 2007 requires sponsors of applicable clinical trials to report results directly to ClinicalTrials.gov within 1 year of completion. The first trials that were eligible

Of Mice, Not Men: When the Bench-to-Bedside Bridge Is Broken

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under this act had to report results starting in January 2018. A cohort study by DeVito et al[6] explored compliance and found that only 1722 of 4209 studies (40.9%) reported results within 1 year, and 2686 (63.8%) reported results later than 1 year. The authors concluded that compliance with this guidance was poor and not improving, likely secondary to lack of enforcement by regulators. Other studies suggested that 50% to 70% of studies registered on ClinicalTrials.gov were eventually published many years after trial completion, but 30% to 50% were never published. The average time to publication for National Institute of Health–funded studies was 2 to 2.5 years after study completion.[7]

Why are negative studies so hard to publish? There is a positive publication bias in the literature, particularly in high impact journals.[8] Studies that are negative or have results that contradict preclinical studies are often not well received by journals or larger conferences. As clinical or translational investigators, some of us have also experienced the (repeated) phenomenon of reviewers questioning the negative clinical results in light of the strong preclinical rationale. High-impact journals with limited space will preferentially accept the “exciting” positive study rather than a summary of lessons learned from a failed study. When negative results of a large phase III clinical study are announced, there is less enthusiasm from investigators, sponsors, and the media to summarize the findings and present them in publication form; there is a preference to focus on more clinically positive efforts. Both sponsors and investigators may seek to delegate funding and other resources to develop and publish more promising therapies. For academic investigators, the publication of negative clinical studies may limit the ability to obtain grant funding for preclinical studies on the same or similar compounds moving forward. Johnson et al[9] contended that although investigators were quick to blame journal editors for being biased against publishing negative results, censoring negative results also came from study funders, in particular pharmaceutical companies, and even the investigators themselves.

Lewis et al[2] powerfully argued that patients make sacrifices to partake in clinical studies when they are not guaranteed any benefit to themselves. Therefore, we owe it to our patients to publish these results to advance science.[2] In many cases, preclinical studies will land in high-impact journals, whereas a negative study may go unpublished or be challenging to find in a poorly circulated journal. Groisberg et al[10] suggested that the clinical trial results should be published in the original journal that reported the preclinical work, regardless of whether or not the results were positive or negative. This is an important, if not a critical, suggestion. Johnson et al[9] expressed that improvement in circulation of negative studies may come from online publications, such as PLOS One, which removes page restraints of printed journals and is committed to publishing any methodologically sound trial.

There are other strong scientific reasons for publishing negative studies. Preclinical investigations that cannot be reproduced continue to remain in the literature, and there is the reality that, without publication of the negative clinical trial, other researchers lose both resources and time pursuing these findings. Furthermore, patients may be subjected to inactive therapies in more than one clinical trial. To stem this waste of energy, patient time, and perhaps even patient lives, the publication of negative data in credible, peer-reviewed journals is crucial. The one important caveat is that a single negative study should not bring a promising concept to a halt. There are many examples of early failed technologies (e.g., antibodies, immunotherapy) that, when pursued and refined, became transformative.

In conclusion, preclinical studies are important and may be the basis of clinical breakthroughs. However, when brought to the clinic, many strong preclinical studies fail—the bridge between the bench and bedside is broken in these cases (Fig. 1). We believe that patients are owed the courtesy and respect of being able to see the results of their clinical trials.[2] We must uphold our part of the unspoken contract between patients and researchers—that is, the return of results to the patients and to the scientific community in reputable, peer-reviewed journals that are accessible.[11] Therefore, we agree with Groisberg et al[10] that the journal that originally published the preclinical work should also publish the results of clinical trials built on that preclinical model. Indeed, this may be even more important for negative than for positive trials because it permits an understanding of the challenges with the original preclinical work and, hence, the construction of a more robust bench-to-bedside bridge.

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