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EDITOR'S PAGE

The Rising Cost of Developing Cardiovascular Therapies and Reproducibility in Translational Research

Do Not Blame It (All) on the Bench

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The rising cost of developing new cardiovascular therapies is not sustainable. In this issue of *JACC: Basic to Translational Science,* Dr. Gail van Norman discusses several of the reasons behind the escalating cost of developing cardiovascular drugs in her paper, "Overcoming the Declining Trends in Innovation and Investment in Cardiovascular Therapeutics: Beyond EROOM's Law" (1). EROOM's law predicts that the cost of developing a new drug doubles every 9 years (2). As in most problems of this magnitude, there are a number of issues that have contributed to rising costs of developing new drugs. Germane to this discussion, a number of recent articles have focused attention on the nonreproducibility of basic and preclinical research (3,4). Indeed, John Ioannidis has stated that "nonreproducibility may be a key reason for the low rate of translation to clinical advances of these seemingly spectacular but spurious biological reports" (4). Although no one would argue about the need and/or importance for reproducibility in basic and preclinical studies, it is helpful to remember that in *Almagest,* Ptolemy argued that the Earth was the center of the universe based on mathematical calculations that were grounded on the repeated observation that the sun rose in the East every morning, and the sun set in the West every evening. Either reproducibility is not what is used to be or inferences drawn from reproducible results do not lead necessarily to the correct scientific conclusion. This begs the question of whether lack of reproducibility in basic and preclinical research is the major explanation for low rate of translation of basic science to clinical advances, and by extension the explanation for the rising cost of developing new cardiovascular therapeutics.

The ultimate goal of cardiovascular researchers is to translate scientific findings into new therapies that favorably affect clinical outcomes. Despite successful preclinical testing, 85% of early clinical trials for novel drugs fail; of those that survive to be tested in phase III trials, only one-half become approved for clinical use (5). Numerous studies have discussed the failure of animal models to reliably predict outcomes for human diseases in clinical trials as an important root cause for the escalating cost of developing new drugs (6). This statement notwithstanding, our inability to effectively test drugs in clinical trials may have more to do with our time-honored paradigms for developing new cardiovascular therapeutics, which may have worked effectively in the past, but have become outdated and impractical. That is, drugs that appear to fail in phase III may actually be effective; however, as stated by Dr. Lillian Siu "we just don't know how to test them appropriately" (5). A study by the Tufts Center for the Study of Drug Development evaluated clinical trials from 2000 to 2009 and found that the 3 most common reasons that drugs or trials fail in phase III were related to efficacy (~50%), safety (~30%), and commercial/financial (~15%) issues (7). Among the phase III trials that were evaluated, cardiovascular and oncology drugs had the highest failure rate. Similar observations were reported by Kesselheim et al. (8) in *JACC: Basic to Translational Science*. The findings of a recent seminar "Why Clinical Trials Fail" held by the European Center for Pharmaceutical Medicine are particularly pertinent to this discussion (**Table 1**) (9). Although "inadequate basic science" is listed as 1 of 6 important reasons for the failure of clinical trials in phase III, a closer inspection of **Table 1** reveals that the major reasons for phase III

TABLE 1 Reasons for Failure in Phase III Clinical Trials

Drivers of Failure	Examples
Inadequate basic science	• Beneficial effects in animal models not reproduced in humans • Poor understanding of target disease biology
Flawed study design	• Patient population definition changed from phase II to phase III • Phase II surrogate endpoint not confirmed by phase III clinical outcomes • Insufficient sample size
Suboptimal dose selection	• Inadequate dose finding in phase II • Poor therapeutic indices
Flawed data collection and analysis	• Phase II "false positive" effects were not replicated in phase III • Overoptimistic assumptions on variability and treatment difference • Missing data, attrition bias, rater bias • Wrong statistical tests, other statistical issues
Problems with study operations	• Data integrity issues; GCP violations • Recruitment, dropouts, noncompliance with protocol • Missing data, unintentional unblinding
Other	• Insufficient landscape assessment of current standard of care and precedents

Source: European Center for Pharmaceutical Medicine; PAREXEL Analysis. Reprinted with permission from Grignolo and Pretorius (9).

GCP = good clinical practice.

failures have to do with problems generated in phase II. Phase II trials are inherently fragile because the number of patients is limited, which limits the number of drug doses that one can study. It also limits the types of endpoints that one can use to gauge clinical effectiveness. Furthermore, phase II trials are often performed in large academic medical centers that serve as tertiary and quaternary referral centers, where the patient population may vary significantly from those studied in larger phase III trials. To overcome the difficulties inherent in phase II studies, some have advocated for combined phase II/III trials or abandoning phase II entirely. Lastly, the failure of therapeutic agent to meet pre-specified clinical endpoints in a large phase III clinical trial does not necessarily mean that the drug is ineffective. A classic example of this is the failure of spironolactone to meet pre-specified primary endpoints in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial. As discussed in *JACC: Basic to Translational Science* and elsewhere, it is likely that many of the patients in TOPCAT either did not take the drug or did not actually have the disease that was being studied (i.e., heart failure with a reduced ejection fraction). A post hoc analysis of the patients in the TOPCAT trial suggested that spironolactone was beneficial in patients in North America, who shared characteristics observed in symptomatic patients with heart failure with a preserved ejection fraction observed in previous clinical trials (10,11).

Reducing the cost of developing new cardiovascular therapies will require fundamental changes in the way in which we conduct clinical trials to make then faster, cheaper, and more adaptable. It will also require changes in the way in which preclinical studies are conducted to improve reproducibility and the way in which journals report new advances in translational research. As stated in the inaugural issue of *JACC: Basic to Translational Science,* "we remain committed to publishing the highest quality translational science, which by its nature means taking some risks on new ideas and early phase discoveries. Accordingly, we recognize that we may occasionally over reach in our enthusiasm to advance new therapies. For this reason, we welcome comments and suggestions from investigators in academia and industry, patients, societies, and all of the governmental regulatory agencies to assist us as we endeavor to guide the *Journal* toward fulfilling its promise of improving outcomes for patients afflicted with cardiovascular disease" (12). To this end, either through social media (*#JACC:BTS*) or by email (JACC@acc.org), we would like to hear your thoughts about how best to balance publishing novel findings against the reproducibility of these findings.

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REFERENCES

1. van Norman G. Overcoming the declining trends in innovation and investment in cardiovascular therapeutics: beyond EROOM's Law. J Am Coll Cardiol Basic Trans Science 2017;2:613–25.

2. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov 2012;11:191–200.

3. Begley CG, Ioannidis JP. Reproducibility in science: improving the standard for basic and preclinical research. Circ Res 2015;116:116–26.

4. Ioannidis JP. Acknowledging and overcoming nonreproducibility in basic and preclinical research. JAMA 2017;317:1019–20.

5. Ledford H. Translational research: 4 ways to fix the clinical trial. Nature 2011;477:526–8.

6. Perel P, Roberts I, Sena E, et al. Comparison of treatment effects between animal experiments and clinical trials: systematic review. BMJ 2007;334:197.

7. Tufts Center for the Study of Drug Development. Causes of clinical failures vary widely by therapeutic class, phase of study. Tufts CSDD study assessed compounds entering clinical testing in 2000–09. Tufts CSDD Impact Report 2013;15(5).

8. Hwang TJ, Lauffenburger JC, Frankin JM, Kesselheim AS. Temporal trends and factors associated with cardiovascular drug development,

1990 to 2012. J Am Coll Cardiol Basic Trans Science 2016;2:301–8.

9. Grignolo A, Pretorius S. Phase III trial failures: costly, but preventable. Applied Clinical Trials 2016;25 [serial online]. Available at: http://www.appliedclinicaltrialsonline.com/print/318912?page=full&pageID=3. Accessed September 24, 2017.

10. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34–42.

11. Bristow MR, Enciso JS, Gersh BJ, et al. Detection and management of geographic disparities in the TOPCAT trial: lessons learned and derivative recommendations. J Am Coll Cardiol Basic Trans Science 2016;1:180–9.

12. Mann DL, Annex BH, Bishopric NH, et al. Introducing JACC: Basic to Translational Science: Why now? J Am Coll Cardiol Basic Trans Science 2016;1:1–2.