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TRANSLATIONAL TOOLBOX

Overcoming the Declining Trends in Innovation and Investment in Cardiovascular Therapeutics

Beyond EROOM's Law

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SUMMARY

Eroom's law (Moore's law spelled backwards), describes adverse trends towards declining innovation and rising costs of drug development over the last several decades. Therapeutics for cardiovascular diseases (CVD) appear to have been particularly sensitive to these trends. Thirty-three percent fewer CVD therapeutics were approved between 2000 and 2009 compared to the previous decade, and the number of CVD drugs starting all clinical trial stages declined in both absolute and relative numbers between 1990 and 2012. In the last 5 years, drugs to treat CVD disease comprised just 6% of all new drug launches. This review discusses the decline in CVD therapeutics, the reasons behind it, and ways in which this trend is being or might be addressed. (J Am Coll Cardiol Basic Trans Science 2017;2:613–25) © 2017 Published by Elsevier on behalf of American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In 1965, Intel co-founder Gordon Moore noted that the number of transistors per square inch on integrated circuits had roughly doubled every year since the time of their invention, and formulated "Moore's Law" predicting that this trend would continue into the foreseeable future. Moore's law is used more generally to describe technologies that improve exponentially over time. In contrast, many indicators dating as far back as the 1950s suggest that rate of new drug discovery is decelerating, and the cost of drug development is increasing despite breathtaking improvements in new drug technologies, such as high throughput screening, combinatorial chemistry, and computational drug design. (1,2). Jack Scannel et al. (2,3) coined the term "Eroom's Law" ("Moore's Law" spelled backwards) to describe the observation that the number of new drugs developed per 1 billion dollars of research and development (R&D) spending is halved every 9 years.

Cardiovascular disease (CVD) accounts for nearly 1 in 3 deaths globally, or over 17 million deaths annually (4,5). That number is expected to reach over 24 million by 2030 as developing countries conquer diseases that impede longevity, and shift their focus toward CVD and other chronic diseases affecting their aging populations (6,7). Despite this, few drugs that truly improve patient outcomes over existing therapies are reaching clinicians and patients, to meet the anticipated growth in CVD (8). Medical innovation faces increasing challenges, including formulation of new ideas, R&D barriers, regulatory uncertainty, growing payer pressures and skyrocketing costs of bringing a therapy to market (9,10). This review

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ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

FDA = Food and Drug Administration

NIH = National Institutes of Health

OD = orphan drug

PPMD = parent project muscular dystrophy

RCT = randomized controlled trials

R&D = research and development

ROI = return on investment

SDLT = severely debilitating or life-threatening

TB = tuberculosis

discusses evidence that medical innovation is in fact slowing for CVD therapeutics, possible reasons for that phenomenon, and ways in which challenges to innovation might be addressed.

THE CVD THERAPEUTICS PIPELINE

Overall, investment in biomedical research and adaptation of regulatory requirements for treatments that meet unmet medical needs has actually been successful in improving productivity for some drug pipelines. Annual new "molecular entity" filings with the U.S. Food and Drug Administration (FDA) were 23 and 41 in 2011 and 2016 respectively, an increase of 78%, and biological licensing approvals in 2011 and 2015 were 23 and 35 respectively, an increase of 67% (11). However, the CVD drug pipeline was a glaring exception to those trends. Most new therapeutics approved by the FDA from 2014 to 2016 were for oncology, infectious disease, and orphan diseases (33, 19 and 19 out of 108 drugs, respectively). FDA approvals for CVD therapies *declined* 33% between 2000 and 2009 compared to the previous decade (7). Just a handful of CVD drugs (11 of 108) were approved between 2014 and 2016 (11).

Industry has responded to the challenges of drug development by refocusing on therapeutic areas that optimize probability of market success, reduce development costs, are more likely to reach rapid regulatory approval and are relatively resistant to pricing pressure (9), thus improving their return on investment (ROI). Those adjustments are negatively impacting CVD therapeutics out of proportion to other clinical areas. Pfizer has 94 clinical product pathways, over one-half of which are devoted to oncology and rare diseases, and only 7 for CVD products (12). Merck has 17 oncology programs versus 2 CVD programs, and Allergan has no CVD programs (12). Based on FDA new drug applications, a "tipping point" in therapeutics occurred around 2008, away from CVD and toward oncology and central nervous system disease (9).

The number of new CVD drugs starting trials of all stages between 1990 and 2012 declined in both absolute and relative numbers (**Figure 1**) (2,13). The percentages of phase I, II, and III clinical trials initiated in 2012 involving CVD drugs were 3%, 3%, and 7%, respectively, compared to 13%, 12%, and 21% respectively of trials initiated in 1990. Around the same period there was a shift from "follow-on" compounds to drugs targeting novel therapeutic pathways (defined as drugs targeting a biological pathway for which the FDA had not yet approved a drug). In 2012, drugs targeting novel pathways constituted 57% of all new phase III trials, up from 27% in 1990. In the last 5 years, drugs to treat CVD, novel or not, comprised just 6% of new drug launches, *down* from 13% in the mid 1990s (14).

Only about one-third of CVD drugs approved since 2000 have a novel mechanism of action (8). Recent regulatory measures favor drugs with novel mechanisms, although novelty does not assure that a drug will meet an unmet therapeutic need or represent a major therapeutic advance, either of which can allow a company to pursue expedited pathways for approval (8). Ward et al. (15) determined that drugs representing true therapeutic advances accounted for just 26% of new drugs entering the British National Formulary between 2001 and 2012. In 2012, Congress approved the Breakthrough Therapy designation program (16), to expedite development of drugs with preliminary evidence of substantial improvement over available therapies. But as of the end of 2016, about 45% of all breakthrough designations were for oncology drugs, and only 2% for CVD therapeutics. Between 2007 and 2015, only 6% of the FDA's fast track designations were for CVD therapeutics, compared to 21% each for cancer and antiviral therapies (**Figure 2**) (8,17).

CHALLENGES IN DEVELOPING CARDIOVASCULAR THERAPIES

Why has the rate of development of new drugs for CVD declined more than therapies for other classes of disease? Some reasons may include: 1) disproportionately low funding of CVD basic research; 2) declining biological targets for CVD therapies compared to other diseases; 3) focus by pharmaceutical companies on target-based research; 4) higher costs of CVD clinical trials compared to other diseases; 5) failures of CVD therapies in late stage clinical trials; 6) lack of strong public advocacy for CVD therapeutics; and 7) failure of CVD researchers and commercial entities to exploit the same regulatory changes that thus far have favored other disease entities over CVD.

FUNDING BARRIERS. U.S. public funding of CVD therapies is disproportionately low compared to the burden of disease. National Institutes of Health (NIH) funding of basic science research for CVD in 2015 comprised only 10% of appropriations, compared to oncology (16%) and allergy and infectious disease (15%) (14). Ringel et al. (14) estimate that there is an approximate 3-fold mismatch in CVD between the burden of disease and the level of U.S. federal