Clapham, J Clin Diabetes 2020, 4:2

Journal of Clinical Diabetes

Short communication Open Access

Six Decades of Drug Discovery: Challenges with Supply and Demand

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Received: April 29, 2020; **Accepted:** May 12, 2020; **Published:** May 19, 2020

Abstract

Six Decades of Drug Discovery in Type-2 diabetes has resulted in the launch of small molecule and peptide drugs from eight classes yet metformin, launched in 1956, is still first line therapy. The huge challenges in discovering and launching drugs in complex diseases such as type-2 diabetes result in many failures due to high attrition. This in turn reflects on the costs of new drugs for these diseases putting pressure on healthcare systems where the impact is most critical in countries with undeveloped or developing healthcare systems but where the incidence of type-2 diabetes will outstrip countries with advanced healthcare systems.

Keywords: Type-2 diabetes; Drug discovery

Drug Discovery

Small molecule drug discovery over the past 60 years has trodden a weary, but doggedly determined path throughout its history from screening drugs in whole animals to the later, post genomic, target-based approaches. The aim of all drug discovery projects, whether target-based, repurposing or random screening, is to deliver a safe and effective therapy that would hopefully beat the competition. Not always the case as evidenced by the plethora of "me too" products across many therapy areas. Drug discovery is hard, there is a huge attrition rate that adds disproportionate costs to companies undergoing this activity and may explain the "me too" approach where there is at least some comfort of market validation and the effort of making a success being down to the company marketing rather than drug discovery teams [1]. The more complex the disease it seems the harder it is to get ground-breaking small-molecule drugs, without a doubt type-2 diabetes is a very complex disease [2-4]. Which may explain why, since its introduction in the mid-fifties, metformin is still a front-line therapy for type 2 diabetes. Diabetes drug discovery over the past sixty was recently reviewed and in that time eight classes of anti-diabetic agents have been evaluated, some still around with more new releases occurring over the past ten years [5]. It is not all doom and gloom, drug discovery is a continuum and new and more efficient ways of doing things will evolve faster as the need increases such as open innovation, industry-academic multi-disciplinary collaborations and of course new modalities such as small-interfering RNA and biopharmaceuticals. There also is a continuous effort in identifying new drugs targets though the target-based approach has its drawbacks [6]. However, at the end of the day decent and predictive target validation is still, in my opinion, the holy grail, particularly for chronic diseases such as type-2 diabetes.

However, the newer, and future, drugs, unlike metformin, are, and will be, expensive. According to the National Institute for Health and Clinical Excellence in the UK liraglutide for example costs around £200 per month in the UK compared to metformin at around £2 per month. We know that the costs involved in bringing a drug to market are massive compared to three decades or so ago. In 2011 cost was estimated to be between 0.3 and 0.9 billion dollars per drug [7]. However, this analysis doesn't take into account costs for the myriad of failed projects which can occur at all stages in the drug discovery pipeline – the most debilitating being late stage failures - which have caused serious productivity issues in the industry [1]. An article in Forbes illustrated this where they divided total research and development expenditure by the number of product launches over a 10 year period [8]. The dreadful reality was that drug discovery in the pharmaceutical industry if not checked would be unsustainable. The numbers then suggest that the giants with greatest loss of productivity were spending in excess of $10bn per drug launch. The industry has been forced to undergo change, often traumatic as many ex-employees will testify, and there is also the risk of retrenching effort away from the high-risk high cost endeavours such as chronic diseases to areas where risk can more comfortably be predicted and managed. This presents a dilemma. In 2013 type-2 diabetes had a global prevalence of 382 million people, forecasted to be 592 million people by 2035 [9]. Of these 80% of type-2 diabetics are likely to be outside the economies with well-developed healthcare systems, including research and development and is a separate topic that is well covered, for example Mohan et al. (2020). A major challenge remains however, how do we provide for these people's future in terms of new drugs [10]?

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