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Innovation in medicine: What does it mean?

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Abstract

Life sciences are facing great challenges. Extramural and intramural research funds from the pharmaceutical industry have significantly decreased in recent years because of the blockbuster and patent cliff problems. In turn, public funds fail to provide necessary support to researchers in North America and Europe. The neuroscience sector is particularly affected given the low rates of success and bearable costs associated with CNS drug development. A question remains though – how to save innovation and who should benefit from available funds if innovation urgently needs to be rescued.

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Editorial

Biomedical research performed by PhDs is well-recognized in the industry and academic sector as the main driver of innovation in medicine. Although there is some confusion in the general public about *medicine* and *biomedical research* or MDs and PhDs, let's simply say that PhDs advance knowledge, whereas MDs apply existing knowledge. In other words, MDs are qualified to clinically apply existing biomedical knowledge which means seeking the right diagnosis and identifying the right treatment for patients [1] whereas PhDs are experts in conducting original fundamental (also called basic research) and translational research aimed at identifying new mechanisms and innovative drugs and therapies that potently act on them [2]. Unfortunately developing a new medicine from bench to bedside has become increasingly risky, long and costly - it may indeed cost up to $2.5 billion dollars and last between 12 and 15 years after discovery (i.e., identification of a drug candidate) to reach market [3]. Many expensive development steps are required by regulatory authorities prior to approval and commercialization of new chemical entities (NCEs) or new molecular entities (NMEs). After discovery, normal drug development processes include safety pharmacology and toxicology tests generally performed by Contract Research Organizations (CROs) specialized in Good Laboratory Practice (GLP)-conducted preclinical testing unlike most academic laboratories.

Preclinical tests include experiments on whole animals and/or reduced animal models (e.g., cultured cells, plasma, etc.) [4]. Given that sufficient data are provided and Investigational New Drug (IND) application is approved, studies in humans (so-called clinical trials) are then authorized by regulatory agencies – that is the clinical studies aimed at gaining additional safety, toxicology, tolerability, pharmacokinetic (clinical phases I-IV) and proof-of-efficacy data in patients (clinical phases II-III) [5]. Specifically, the phase I trial (> 50 healthy volunteers) uses designs such as dose escalation, randomization, placebo-controlled and blind testing to identify dose-dependent adverse events, therapeutic window, toxicology, tolerability, drug-drug interactions, and maximum tolerated dose (MTD), to name a few (www.fda.gov) [5-7]. In larger cohorts (phases II-IV), some of these data remain to be collected for further details about the effects of repeated administration and long-term use. Phase II and III trials are largely about gaining evidence of efficacy – increasingly large cohorts

of volunteered patients need to be recruited – the Phase II trial typically seeks the recruitment of 50-150 volunteers whereas the Phase III may recruit 500-2000 volunteered patients in order to clearly demonstrate statistically the extent to which a drug candidate fulfills the targeted unmet medical need in patients.

Funds typically used in medical research for innovation come from governmental agencies such as NIH in US, ERC in Europe and CIHR in Canada. Substantial funding has also traditionally come from the industry. Unfortunately both types have significantly decreased in recent years. Evidence-based medicine and repurposing and repositioning old drugs which don't lead to innovation have also increasingly attracted funding towards MDs instead of PhDs - basic research funding in the US decreased by 50% between 1997 and 2012 (approximately from 55% to 25% of available research funds) whereas clinical research increased by two-fold during the same period (approximately from 8% up to 20% of available governmental research funds) [8]. The golden age of the pharmaceutical industry is past according to several experts. In 2011, Mark Kessel wrote in Nature Biotechnology: 'Is there any doubt that the leading drug companies are in desperate need of reinvention? Blockbuster drugs are coming off patent or being taken off the market for safety reasons and there are no replacement drugs on the horizon to make up the shortfall in profits. To state the obvious, over the past decade, the pharmaceutical industry has brought few drugs to market from its own development efforts.

Commentators have stressed and heads of big pharma have acknowledged that the sector's R&D efforts need to be drastically changed' [9]. More specifically, the worldwide crisis in 2008 and the patent cliff problems have had a devastating impact on the industry. Pharmaceutical companies have announced 156,000 jobs lost in the United in recent years [10] and global sales of prescription drugs have drastically decreased [11] whereas so-called Big Pharma such as GSK, AstraZeneca and Novartis have decided to significant decrease or even cease research activities in neurosciences [12]. In those conditions, what is left for innovation? Well, it is hard to say. Things have to change to say the least. For instance, public research funds should stop being driven away from PhDs to be 'lost' in expensive physician-initiated trials already extensively supported by Big Pharma [13]. Also, the traditional 'one-target-one-disease' principle leading to NCEs and NMEs, extensively used in the industry and often by academic researchers, has become too expensive and awfully risky – it could advantageously be replaced by the multi-target approach using existing molecules [14] – i.e., new drug combinations, using existing or old drugs, or so-called fixed-dose combination (FDC) products for innovative drug treatments are already being developed in therapeutic areas such as asthma, HIV, cancer or diabetes (e.g., Atripla®, Advair®, Janumet®, etc.) [15,16].

Now, the question is – will both the industry and governments take the right decisions to stimulate again innovation? Let's hope they will because ageing and ageing-related health problems are increasingly problematic for the entire health care sector (e.g., governments, insurance companies, users, and pharmaceutical companies). According to the World Health Organization, the number of people aged 65 or older is projected to grow from 524 million (2010) to nearly 1.5 billion in 2050 (who.int/ageing). Most of the ageing-related diseases (e.g., cancer, cardiovascular, metabolic and chronic diseases, Parkinson's disease, Alzheimer's disease, dementia, etc.), particularly in neurosciences, are still in most cases considered essentially as unmet medical needs desperately seeking for real potent first-in-class drugs and biologics.

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