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Are new drug combinations a solution to both the patent cliff and lack of new CNS products?

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Financial crisis of 2008 and patent cliff challenges

Until recently, the modern pharmaceutical industry has never stopped growing since the mid-1800s. Drugs such as morphine, quinine, amphetamine, antidepressants, barbiturates, insulin, anti-inflammatory drugs and many others have generated extensive revenues for the so-called Big Pharma [1]. Unfortunately, several significant changes have occurred a few years ago. The 2008 worldwide crisis has both decreased market capitalization and levels of private equity financing access for several biopharmaceutical companies. The industry also announced huge layoffs in the U.S. with 156,000 jobs lost between 2009 and 2013 [2]. Global sales of prescription drugs began to drastically in 2011 [3]. The end of the blockbuster-drug era became all of a sudden a reality reinforced primarily by the so-called patent cliff problem – generally defined as the phenomenon of patent expiration dates and an abrupt drop in sales that follows [3,4].

Lack of CNS products – urgent need for new drugs for neurologically impaired patients

Beyond those significant financial issues, many other more specific problems have emerged. For instance, a decline of discovery associated with unsustainable increases in cost of development of new chemical entities (NCE) and new molecular entities (NME) or an increase of competition from generics drugs [5]. The field of CNS drug development has been particularly affected by these problems. Several reasons may explain that.

Firstly, it is generally recognized that most of what is currently known about CNS disorders including breakthroughs made since the 1990s have typically failed to translate into new or more effective drugs for patients suffering from these disorders [6].

Secondly, in the past few years, several high profile pharmaceutical companies have decided to cease major research activities in neurosciences (e.g., GSK, AstraZeneca and Novartis). The major reasons are that the development of new psychotherapeutic NCE/NME drugs has become more and more a high-risk activity with low approval rates [7]. Some experts says that CNS drug development can cost billions more than any other therapeutic area, yet has a 45% higher chance of failure than drugs targeting other disorders [8].

Thirdly, the high risk and low approval rates of CNS drugs have sent billions of dollars down the drain in recent years forcing Big Pharma to be turning its back on further CNS drug research.

Consequently, most CNS diseases and disorders remain still today, largely unmet medical needs. They significantly outnumber diseases in other therapeutic areas, inflict higher treatment and loss of productivity costs (i.e., compared with cancer or diabetes) and are growing in incidence faster than any other disease class in Western countries. In Europe, 38% of the population is affected by CNS disorders whose burden in 2010 was around 798 billion euros [9]. An additional 20% increase is expected in the next coming years [10].

Lessons from research in other areas

In the fields of cancer, HIV, or asthma, a clear trend has emerged nearly twenty years ago to sustain innovation. Drug combinations have indeed been progressively recognized as some of the best therapeutic strategies to meet the needs associated with these complex medical problems. Drugs such as Atripla (emtricitabine/tenofovir/efavirenz) against HIV, Advair (to fluticasone/salmeterol) and Symbicort (budesonide/formoterol) against asthma or Janumet (sitagliptin/metformin) against diabetes have become blockbusters and, in some cases, gold-standard therapies. Drug combinations such as these, often known as a fixed-dose combination (FDC), are essentially products that include two or more active pharmaceutical ingredients (APIs) combined in a single dosage form, which is manufactured and distributed in fixed doses [11]. They may include one or several NME or be composed only of so-called 'old' off-patent molecules.

Their development has drastically increased recently in the U.S. According to PharmaCircle research, the number of

FDC approvals has more than tripled over the last decade compared to the early 1990s. There is increasing evidence suggesting that developing FDCs as new and first-in-class therapies against CNS disorders may also be possible. In fact, as of 2013, according to a study from Drug Development, FDC products for various CNS indications count for 22% of the pipeline products currently in development by the industry.

Urgency for neurobiologists to further practice out-of-the-box thinking

Beyond the significant unmet medical needs of CNS disorders, the higher risks of developing CNS drugs, and the problem of most neuroscientists in exploring the potential of FDCs, there is the traditional belief shared by many neurobiologists still today: the 'one disease, one target and one drug' dogma. There is emerging evidence suggesting that the CNS, probably the most complex organ of our body, is not ideally suited for this approach and shall benefit from therapies that concomitantly act upon several targets such as FDCs.

Indeed, it is well-known that the CNS comprises multiple parallel pathways and a plethora of intracellular signals. Extensive plasticity changes and adaptations are also known to occur after CNS trauma. Drug treatments such as FDCs capable of reactivating or modulating the activity of several targets are thus likely to be particularly potent for CNS dysfunctions, as demonstrated already for drug combinations against HIV, cancer, cholesterol, or asthma.

In fact, some evidence has been found in our laboratory recently. Indeed, while no single molecule, used separately as a monotherapy, has ever been found to potently restore locomotor activity in animal models of paraplegia was found 10 years ago by my team. It is a tritherapy called Spinalon™ that can enable synergistic actions upon several cellular targets associated with spinal locomotor neuron activity for temporary induction of episodes of basic walking capabilities in chronic paraplegic animals [12,13]. A similar approach, applied instead to bowel and bladder problems, was found also in our laboratory to elicit on-demand spinal-generated episodes of micturition and defecation in neurologically impaired animal models [14]. If approved, these FDC products may eventually constitute first-in-class therapy against paralysis, urinary retention and chronic constipation, respectively.

Concluding remarks

Using known and safe molecules (e.g, generic off-patent molecules) for the design of new FDCs should be further explored specifically in neurobiology and CNS research to accelerate and ease the development and approval of potent first-in-class therapies that shall meet the critical needs of neurologically impaired patients. Beyond these medical reasons, leaders in this industry shall be reminded that FDCs are typically considered as low-cost, low-risk projects [15] with revenues that are increasingly protected legally by regulatory authorities such as the FDA that recently approved between three and five years of extended exclusivity rights in some cases [16].

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