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The process of drug discovery and the Yin/Yang of small-molecule/biotech option

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ABSTRACT

Until the mid 90ties of last century, talking about drug discovery and development was essentially referred to the process of discovery and development of small-molecule chemical entities. All the language, common procedures and technicalities were inherent to this setting; concepts such as drug design, hit and lead compounds, high-throughput screening were referring to the typical mode of investigating and selecting small-molecule candidates through pre-clinical development. At that time, the arrival of the first biotech drugs has markedly changed the landscape, requiring a completely new approach to pre-clinical development. Issues related to drug-receptor interaction or to the selection from a huge number of candidates were obviously simplified to a minimum compared to the small-molecule setting. Conversely, the pharmaceutical development of biotech drugs showed far higher complexity, and the overall high complexity of industrial production initially represented a major issue to justify the high costs of biotech drugs.

Besides, the technical impossibility to make 'generics' of biotech drugs was another strong reason driving Pharma companies toward the development of biotech drugs. Thus, in the beginning the early development phases of small-molecules or biotech drugs really stood as two distant planets. However, by the time such initial distances have been progressively reduced. From the biotech site, the technique of phage-display library scanning and similar approaches made the selection of biotech lead compounds resembling more closely what happens with small molecules; also the complexities and high costs of pharmaceutical production have progressively reduced their impact. On the other site, the impressive progresses of basic knowledge on the human kinome and other relevant fields of molecular and cellular biology made possible that today we have small-molecule drugs targeting the same pathologies once specifically targeted by biotech drugs, MoAbs in particular.

Another factor (albeit not related to drug development) with an important role in reducing distances between small-molecule and biotech drugs has been the novel approach to estimate the value of drugs, and therefore their prices. Since nowadays the major drive fixing the value (and costs) of new drugs is the added value for human health, any difference related to the costs of production has been greatly reduced, and we have today several high-cost small molecules along with their sibling biotech drugs.

Last but not least, biotech drugs can be 'copied' as well, since we now have biosimilar drugs, although the pathway to develop copies of biotech drugs remains steeper compared to that leading to the equivalents of small-molecule drugs.

The first marketed recombinant-DNA-derived ('biotech') drug was human insulin, produced by Eli Lilly and Co. The drug was approved by UK regulators in September 1982 (there was no EMA at that time) and soon after by the FDA, in October 1982 [1]. We have now the second generation of biotech drugs, with the first generation being represented by endogenous proteins and glycoproteins, including insulin, erythropoietin, G-CSF and growth hormone. The second generation involved a further increase in the level of complexity, in terms of 3-D structure and increased costs/risks ratio (in manufacturing, regulatory scrutiny and higher burden of proof), and started in 1986 with the commercialization of the first therapeutic monoclonal antibody (MoAb), Orthoclone OKT3, approved for prevention of kidney transplant rejection. It took more than 10 years for the second MoAb, daclizumab, to arrive on the market in 1997; from then on, the number of MoAbs and other second-generation biotech drugs available on the market grew very fast. A recent survey reporting the performance of Pharma R&D in 2015 shows that biotech companies spent 40.1 billion of US dollars on R&D in 2015, out of a total of 58.8 billion on R&D for the whole Pharma sector, meaning that 2/3 of all the investments and efforts in Pharma R&D are put today on biotech drugs [2]. I quoted the above few data, spanning from the beginning of the story to the present time, to resume at a glance the huge changes brought about by the arrival of biotech drugs on the Pharma scene.

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Until the mid 80ties of last century, the concepts of drug discovery and development were essentially referring to the process of discovery and development of small-molecule (SM) chemical entities; all the language, common procedures and technicalities were inherent to this setting. Such terms as drug design, hit and lead compounds, high-throughput screening were related to the typical way of investigating and selecting SM candidates through the pre-clinical phase of development. The arrival of the first biotech drugs markedly changed the landscape of drug R&D as well, requiring a new approach to pre-clinical development. Issues related to drug-receptor interaction or to the selection from a huge number of candidates were simplified compared to the SM setting. Which was the standard pathway of drug discovery and development before the biotech era? Firstly, we should consider that the human genome project was not completed yet [3]. Usually the first step in drug discovery was the characterization of a receptor-ligand system (sometimes only a ligand-orphan receptor, or vice versa), and the 'direction' of such discoveries was obviously from-phenotype-to-genotype. Once a receptor-ligand system was discovered and characterized, then a series of agonist and antagonist compounds could be generated, and the chase started trying to ascertain whether these molecules might be useful as drugs. It was a time-consuming and inefficient approach, that we might define here as the 'trawl-net fishing' model. The bridge between the biology of a receptor-ligand system and its pharmaco-therapeutic exploitation was often represented by the localization of the receptor. This was the case for several receptors found within the central nervous system (CNS), such localization being per se sufficient to suggest the possible involvement of the receptor-ligand system in such human disorders as depression or anxiety. To make but a few examples, this occurred with the neuropeptide corticotrophin-releasing factor (CRF), whose localization in the brain is reminiscent of those of monoaminergic neurotransmitters [4]. This system was thoroughly investigated in pre-clinical models, translating decades of research into the robust hypothesis that the blockade of CRF receptors in the CNS might have therapeutic relevance in human anxiety and depression [5]. It was therefore quite frustrating to learn from the subsequent clinical trials that specific antagonists of CRF have no clinical efficacy in these disorders [6,7]. A similar story occurred with neurokinins and their receptors, which were initially postulated to have a role in human nociception, anxiety and depression [8], ending up in the niche therapeutic use of NK receptor antagonists as *anti*-emetics in combination therapies [9]. Luckily, there have been also several examples of fruitful chase, especially if the newly discovered receptor was unambiguously related to a specific patho-physiological mechanism, as with drugs blocking histamine type-2 receptors or angiotensin converting enzyme, to name but a few.

Not only the trawl-net fishing model was inefficient for the above explained reasons, but also because of the need to select the best drug candidate among a huge number of molecules. Such selection involves a first step assessing drug-receptor interactions, either via the high-throughput screening approach or the virtual drug design [10,11], which is leading up to the downstream in vitro or in vivo models investigating putative therapeutic efficacy.

How this scenario changed after the arrival of biotech drugs, the MoAbs in particular? If one develops a MoAb, this will be directed against a given antigen; the relevance of such antigen to an underlying patho-physiological mechanism is usually known in advance. Thus, it is possible to foresee the therapeutic utility of the new drug from the beginning. This describes, in plain words, the concept of 'target therapy'; in fact, such concept, which is today widespread diffused and even fashionable, was born with the introduction of therapeutic MoAb. It took quite a long time to develop the technological bases for the production of therapeutic MoAbs on an industrial scale. A fundamental step was represented by the hybridoma cell technique described by Kohler and Milstein in 1975 [12], which first allowed to have sufficient amounts of MoAbs to be tested in biological screenings. As stated above, the full clinical exploitation of these techniques took place about 20 years after, in the mid 90ties. At that time, the two conceptual models of drug development, i.e. the trawl-net fishing model associated to SM drugs and the target therapy model associated to MoAbs, were very different and distant from each other, justifying the reference to the Yin-Yang opposites mentioned in the title of this commentary. By the time, the two models tended to converge toward a common pathway, not only as far as drug discovery and development are concerned, but also for other aspects such as drug pricing, 'copiability' and clinical settings of utilization. Therefore, at present the Yin-Yang opposition between SMs and biotech drugs has been greatly reduced, as it will be discussed next.

As of today the 'trawl-net fishing' model is less and less applied, while on the contrary the target therapy model is applied as far as possible to identify druggable targets for biotech as well as SM drug candidates. This normally occurs in oncology, with a steadily increasing number of SM kinase inhibitors [13]. It also happens that the same signaling pathway involved in cancer cell proliferation may represent a target for MoAbs at the receptor level, and for SM kinase inhibitors at downstream signaling level [14]. While SM drug candidates share with biotech drugs the target therapy approach, the latter by the time became more similar to the SMs as far as the screening to identify lead compounds is concerned. This process started with the introduction of phage-display libraries and similar techniques able to select a MoAb with given features (e.g. high binding affinity, ability to trigger complement- rather than antibody-mediated cytotoxicity, etc.) out of a host of MoAbs developed against the same antigen [15]. Indeed, it should be considered that antigens present a number of epitopes, and MoAbs can be developed against different epitopes of the same antigen. On this regard, an interesting paradigm is represented by trastuzumab and pertuzumab, two MoAbs both directed against HER2 membrane receptors but inhibiting signal transduction via different mechanisms (inhibition of dimerization-independent and –dependent signaling, respectively), which translates into an increased clinical efficacy of the MoAbs given in association compared to trastuzumab alone [16]. Nowadays it is even possible to screen MoAbs and other glycoproteins for their profile of glycosylation, which may greatly affect binding affinity, pharmacokinetics and other relevant features of the drug [17]. Thus, although the technological approaches may be different, at present biotech drug candidates undergo screening processes that are reminiscent of the high-throughput screening typical of SM compounds.

The industrial production of biotech drugs is far more complex compared to that of SMs. 'The product is the process' is a frequently-quoted aphorism used in these cases to summarize and emphasize such complexity [18]. Among other consequences, the production of biotech drugs in industrial scale caused a huge increase in the costs of production compared to previous standards. Regardless of whether one was referring to a free-price or to a controlled-price system, in the mid 90ties the cost of production was a primary component in the determination of drug prices; therefore, biotech drugs soon became a paradigm of high-price products. Conversely the costs of production for SMs of chemical synthesis were very low in comparison. Thus, looking at the scenario in the mid 90ties, the Yin-Yang concept was fully adequate to describe the differences in price existing between biotech and SM drugs. By the time the rules and criteria to establish the price of new drugs have largely evolved. The costs of production have lost much of their initial relevance (indeed, technological progress allowed to reduce the costs of biotechnologies during these years). Conversely, a higher consideration has been progressively given to the overall R&D costs of the Companies; on this regard R&D costs, especially the costs of clinical trials, underwent a marked increase in the last decades, which was largely independent from the type of drug –whether a biotech or a SM- under development [19]. Perhaps more important is yet another factor, i.e. the added value in health brought about by the new therapy. This concept, whose relevance can be grasped by intuition, by the time has been given a quantitative dimension, with such issues as the cost-effectiveness analysis or the quality-acquired-life-year (QALY) and its

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