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Genomic Chemistry: A New Way of Thinking Drug Discovery

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ABSTRACT

Time has come for drug discovery and development of small molecules therapeutics to integrate genomics early in the drug discovery process .Through few significant examples, the manuscript highlights the need to take on board genomics issue in the medicinal chemistry process. If medicinal chemistry does not evolve, the question of spending decades to develop new drugs will raise, since other omics therapies will provide efficient treatments, less expensive and safer.

Keywords: Genomic chemistry, immunotherapy, cancer, neurodegenerative diseases, drug discovery.

INTRODUCTION

Since the first synthesis of urea by Wohler in 1828[1], during decades chemists have made creditable efforts of creativity to develop innovative synthetic methodologies, to offer more and more safe and efficacious drugs to prevent and cure human diseases and sometimes with the secret hope to find one day the long life elixir. Unceasingly like painters, or sculptors, they have always tried to improve, expand and adapt their art for the wellness of humanity. It was not an easy task. After long and expensive clinical trials under the control of pharmacologists and physicians, drugs which overcome with success these clinical trials, were prescribed to men community. In this context creative medicinal chemists were pride to be the key actors of that central science. Starting from fundamental natural building blocks like amino-acids, nucleic bases, natural fatty acids, chemist designers have built fantastic architectural molecular edifices which can be seen as true works of art. Remember the first synthesis of vitamin B12 by Woodward (Nobel prize 1972) which represented a real achievement [2] At that time ‘’*molecular, cellular, genomic*’’ biology were not as developed as to-day, these ‘’*omic sciences*’’ were in their infancy. For the chemist community it was still the blessed time to develop drugs to cure any of diseases which strike human being health on earth. Yesterday medicinal chemistry was mainly based on the knowledge of few fundamental concepts derived from:

***Enzymology*:** the design of competitive, non- competitive, uncompetitive or irreversible enzyme inhibitors led to the discovery of potent clinically used drugs such as *Lipitor* (Atorvastatin) an HMG-CoA inhibitor used as anti-cholesterol drug [3]

***Receptors* :** the design of agonists, antagonists or inverse agonists specifically binding to topographically well-characterized receptors, has led the discovery of important drugs such as *Plavix (Clopidogrel),* an antithrombotic drug which binds to the ADP receptor [4]

Ion channels ligands: Potent drugs (ions, small molecules, toxins or venom) have emerged from the knowledge of the ion channel mechanisms. Norvasc (Amlodipine) [5], a potent anti -hypertensive drug, or *Nexium (*Esomeprazole)[6]. a proton pump inhibitor used as anti-ulcer drug, are significant examples.

The full understanding of these concept allow to teach medicinal chemistry into a rational and coherent didactic discipline and help rational drug design. To- day, understanding drug action at a molecular level, is not sufficient. It is time for medicinal chemists to consider drug design at cellular or organismic levels.

Why reorient the development of medicinal chemistry paradigm?

Pharma companies routinely spend hundreds of millions of dollars on developing drugs only to see more than 90 percent of them, fail in clinical trials or later. It becomes obvious to change the drug discovery approach. Only highly promising drugs at late stages of development should be checked out on humans in clinical trials. But economic and ethical reasons make that approach impossible in the early stages of drug. This is the reason why new drugs are tested on animal or on cultured cells. Unfortunately experiments on non- human models and their tissues are notoriously problematic, even if they have historically been the best available option. Animal’s physiologies don't always respond to drugs exactly as the human body would; moreover, not all human diseases have good animal models [7].

The case of Alzheimer’s disease (AD) research is highly significant**.** In 2010, there were between 21 and 35 million people worldwide with AD [8] .Unfortunately, to day, no efficacious drugs for the treatment of AD are available, but if they were, to whom would they be prescribed?

-To patients in the early stages of the disease to circumvent further development?

-To patients already at an advanced stage of the disease?

These questions are difficult to answer .Once a patient has been clearly diagnosed with AD, the prospect of restoring their normal neuroplasticity through the use of drugs becomes uncertain for a majority of neurobiologists. Because of the great challenge and high risks associated with CNS drug discovery and development, several major pharmaceutical companies are exiting or depriorizing CNS drug search in response to investor pressure [9].

In front of this situation and in order to overcome those major

problems, research on AD therapy will progressively reorient towards immunotherapy (vaccine) or gene therapy [10]. It will become more likely that future medicine will turn more and more to biotechnologies, leaving medicinal chemistry by the wayside, consequently *cellular therapy* and more specifically *stem cells therapies* will be used to treat or to prevent some specific diseases. Research is underway to develop various sources for stem cells(bone marrow transplant or umbelical cord blood) which will constitute stem cell treatments for neurodegenerative diseases, diabetes, heart disease. As an example ,regeneration of damaged tissue in the back of the eye (retina stem cell therapy) [11] is a significant sign that biotechnologies will represent the to-morrow therapies.

Today both chemotherapy and genomic therapy are on the road. Chemotherapy is still dominating but genomic therapy is spirit to rapidly remake its delay. Probably for a while both ways to prevent and to cure men's diseases will be used in an integrated manner , but in the future, genomic knowledge rapidly progressing will become the central science to which human beings will resort to look after their health evils. Cancer and neurodegenerative diseases are excellent examples of how medicinal chemistry and biotechnology should cooperate to promote the best and most cost effective treatment for these diseases.

Biotechnology and cancer

Around 40 new anti-cancer drugs are in clinical development, and nearly a dozen of them are in phase III testing around the world ,but in the same time U.S. Food and Drug Administration approved therapeutic cancer vaccines that treats malignancy by turning immunity against it .I*pilimumab (Yervoy),* which accelerates antitumor immunity in patients with metastatic melanoma is a significant example [12] .*BiovaxID*, is a cancer vaccine in phase III which lengthens disease-free survival in patients with follicular lymphoma by an average of nearly 14 months, with virtually no side effects [13]. **.**Scientists attribute this success to a better understanding of how tumors fight off the immune system. If progress continues, immunotherapy will increasingly be used to prevent tumor recurrence in patients who complete first-line treatments. Ideally these vaccines will attack any new cancer cells, while leaving normal cells alone. Unfortunately immunotherapies, which don't target tumors directly, have first to turn on the immune system against cancer, which takes longer to work than actual drug chemotherapy treatments.

Biotechnology and neurodegenerative diseases .

No efficient drugs against motor neurons diseases like Spinal Muscular Atrophy (SMA) and Amyotrophic Lateral Sclerosis (ALS) are actually available. Medicinal chemists from a small pharma are trying to find new small molecules able to tackle this rare disease .After 15 years of research and development, this small pharma reports recent promising results from clinical trials which let foresee the possible approval of first drug against, Survival Motor Neuron (SMN) protein which is the major cause of SMA [14] .At the same time in 2008 researchers from Harvard University and Columbia University have succeeded to generate iPS (induced Pluripotent Stem) cells from a 82 years old woman diagnosed with a familial form of ALS. Those iPS cells , have been successfully directed to differentiate into motor neurons, which are destroyed in ALS[15] **.**From these results it could be anticipated that cellular therapy could be rapidly applied for the treatment for this rare motor neuron diseases .

From these examples, one can ask the question if it is still worthy to spend decades to develop new drugs if biotechnology processes (cellular, gene or immune therapy) can provide efficient treatments, less expensive and more safer than traditional drug therapy?

Chemical genomics as a starting point for drug discovery

When Watson and Crick discovered 60 years ago that our bodies were coded in genes, it was an accomplishment with deep and lasting impact but now science has connected genes and disease. Hard wired in our chromosomes are instructions to make drugs work, fail, or produce side effects. The human genetic code appears to be the key to health and to disease. From families where everyone lives into their 90s, genes which make resistant to illness were progressively identified while in parallel through siblings with the same illness, genes which increase the risk of specific disease were pinpointed. As a consequence gene therapy and cellular therapy appear the most appropriate therapies to diagnose, to treat and hopefully to cure human diseases .At the same time, patient personalized chemotherapy could emerge if medicinal chemists integrate early in their drug discovery approach, genomic elements through the use of gene or protein microarrays techniques. Indeed DNA microarrays have proven very useful in elucidating the functions of the drug biological targets [16]. By comparing the differences between the profile before and after drug treatment, genes whose expression are modulated by the chemical ligand, can be identified. Those information can often reveal specific transcription factors and other regulators for each pool of genes, while genetic study interactions can unravel the genetic basis for drug sensitivity. Some cancer cells are more resistant or prone to certain anticancer drugs; therefore drug sensitivity profiles for different type of cancer, will be developed starting from genes, which expression involved specific biological pathways in which the drug interfere. Hence for a patient suffering of a given pathology knowing its own genomic profile, and knowing the ability of some drugs to deregulate genes, selected drugs will be prescribed to him, alone or in combination with immunotherapy treatment. If genomic chemistry is incorporated early in drug discovery process, the next futuristic reorientation for medicinal chemistry will be how to find ways to bridge living (cellular and gene therapy) and nonliving (classic chemical drugs) systems?

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