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GUEST EDITORIAL

Modern drug discovery and the Indian opportunity

New drug discovery being a complex and interdisciplinary enterprise has remained in continuous focus due to its great successes as well as failures. The current global drug discovery model has been remarkably successful in harnessing the basic scientific research in discovering novel life-saving drugs and biopharmaceuticals, which led to dramatic improvements in the quality of life in last 100 years. In addition, it led to newer insights in disease biology. Much of the credit for these achievements must go to the great scientific synergy between the leading universities, medical hospitals and pharmaceutical companies in the western countries, supported by enabling regulatory and market mechanisms. Ironically, this synergy never materialized in independent India; testified by the fact that the track record of the global regulatory approval of new drugs discovered in India has been dismal at best. From the quick overview of the history of drug discovery (USFDA Orange Book), it will be obvious that most of the first-in-class drugs (antibiotics, anticancer, antidiabetic, CNS, blood-pressure and cholesterol lowering, immunosuppressant, antimalarials, etc.) emerged out of fruitful collaboration of the disciplines of synthetic chemistry, pharmacology and medicine. This model has been particularly successful in the US because of the structured vicinity of basic research and medical science, under one institutional ecosystem – the US medical schools. On closer examination of the discovery paradigm, another remarkable feature stands out; contributions of various traditional systems of medicine. If one follows carefully the scientific threads of the discovery of most of the first-in-class drugs, root of the discovery invariably will lead to a traditional system of medicine (Indian, Chinese, African or South American) or long-standing empirical observation. Initial natural products leads are invariably modified by medicinal chemistry to achieve desired safety and efficacy. Perhaps one of best examples of this is the first natural product statin (mevastatin) discovered from a fungal source in Japan, followed by the development of currently used blockbuster cholesterol-lowering drug atorvastatin (lipitor). The journey of synthesis of natural products isolated from medicinal plants or micro-organisms, e.g. atropine, asprin, quinine, morphine, reserpine, cyanocobalamin, cyclosporine, FK-506, rapamycin, gingkolide, camptothecin, colchicine, vincristine, brevitoxin, azadirachtin, etc. have been remarkable and breathtaking, enriching organic chemistry as well as interfacing biological sciences (nucleic acids, proteins, carbohydrates, lipids, vitamins, hormones, neurotransmitters, etc.) and physical sciences (new materials, catalysts and concepts). However, its greatest impact on human well-being has been in the area of new drug discovery. Over 90% of currently used medicines are small molecules discovered and enabled by the art and science of natural products chemistry and organic synthesis. The case studies of some of the approved drugs such as fingolimod, eribulin, yondelis, velcade, alandronate, varinostat, kinase-inhibitors, ACE inhibitors/ARB antagonists are quite illuminating.

However, almost for a decade now (2000 onwards), this successful engine of new drug discovery has hit the roadblock and some sort of crisis is brewing up due to the empty-pipelines, innovation-deficit, failed promise of new technologies like combinatorial chemistry, current block-busters coming off-patent, withdrawal of approved drugs from the market due to serious safety concerns, and arguably more stringent regulatory environment. However, this global productivity crisis in drug discovery should not be used to support the oft-quoted arguments that global pharma companies have lost the core competence. This crisis has been hotly debated within the pharmaceutical companies and the scientific community. Excellent commentaries have been written on this pressing issue and specific reasons, both scientific and managerial, identified for the slowdown in the new drug approvals. Ironically this dire situation has arisen at a time when the most revolutionary advances in basic biology, chemistry and technology have been made. The response to this situation necessitated major restructuring (cost-cutting and down-sizing of R&D, and mergers and acquisitions) of almost all big pharma companies. However, a recent analysis showed that none of the above measures has actually helped. Consequently, this crisis led to the emergence of a new business model of global drug discovery based on outsourcing of early stage R&D work to a new set of companies taking shape in emerging countries (like India and China). There is hope and expectation that the current crisis of innovation-deficit will be bridged by forging partnerships with start-up companies and contract research organizations (CRO) in the emerging countries. And, arguably with the rise of

scientific capabilities in India and China, the focus of new drug discovery itself will shift to the East. But for this to happen, a proactive policy and funding mechanism will have to be created.

Therefore, the current crisis in global drug discovery presents a unique opportunity for fueling scientific innovation in India and China. The key question whether the science and business leadership of these two counties will recognize this opportunity to bring this interesting premise to success, however, remains. A lot has been written about this global economic shift from the western perspective; but the viewpoint and strategy from the receiving end (India and China) have not been sufficiently articulated. India today presents an interesting case study for analysing successes and failures of scientific research in addressing healthcare needs of a developing economy. The country has some of the best healthcare facilities and hospitals comparable to the best anywhere else, but affordable to a small privileged population. The majority is still stuck deep in poor, crumbling and uncaring health care system, the situation further complicated by heavy burden of diseases such as malaria and tuberculosis. In spite of some major strides made by Indian science and technology (agriculture, space, atomic-energy and information technology), the track record of innovation in the area of new drug discovery has been pretty dismal; even with a large scientific workforce and infrastructure in chemistry, biology and medical sciences. It is important to understand the historical perspective of how things came to the current status. The single most important factor responsible for the state-of-affair in new drug discovery being the change in Indian patent laws in 1970, which de-recognized the validity of the product patents and allowed Indian companies to market patented drugs of western pharmaceutical companies. Arguably, this landmark legislation did significant social good, providing cheap and affordable medicines to the large segment of poor population, and laid foundation of generic pharmaceutical industry in India. However, predictably, it removed incentive for discovery of new medicines and diagnostics, and effectively drove innovation out of R&D in two important ways. Following this legislation, almost all western pharma companies decided to close down or sell their R&D centres in India in late 1970s. On the other hand, the drug discovery-related research (natural products and medicinal chemistry, new target identification, pharmacokinetics, metabolism, toxicology, preclinical and clinical studies, etc.) got de-prioritized in science departments of the universities and national laboratories. The major fallout of this was felt in chemistry research leading to the loss of long-held leadership position of India in natural products chemistry and pharmacology, a primary source of 'first-in-class' drug prototypes. The emphasis shifted to total synthesis of known natural products and new synthetic reagents/methodologies.

India rejoined international patent regime in 2005, after a gap of 35 years. Post 2005, India finds itself in a unique situation. It has a number of scientific institutions with excellent chemistry and biology research, a successful generic drug industry but with poor skills and capabilities in new drug discovery. However, one remarkable development, post 2005, provides a missing piece of the jigsaw puzzle, which might address the 'culture-gap' of new drug discovery in India. This relates to the emergence of a number of companies and organizations providing a variety of services (ranging from bioinformatics, structural biology, drug-design, medicinal chemistry, ADME-Tox, preclinical and clinical trials) to global pharmaceutical companies. This new breed of companies and institutions, the CROs, are well equipped with trained manpower and research infrastructure meeting rigorous regulatory standards of the US FDA. Curiously the skill gap created during the process-patent period (1970–2005) has been partly filled in a rather short period of time by these companies providing discovery, preclinical and clinical services. These developments shift focus and responsibility back to Indian scientific universities and institutions, medical hospitals, funding and regulatory agencies to take advantage of the realities of the new world. The challenges are how to re-focus in creating enabling discovery ecosystem, partnerships, mechanisms and regulations. Having said that, this indeed seems to be a tall order, but it will happen. It is the premise and prediction of this author that in next 10 years, India will become a hub of new drug discovery, because all the critical ingredients are in place. Some of the key issues meriting attention include (a) harnessing power of natural products chemistry and modern analytical tools in exploring medicinal plants used in various Indian systems of medicine; (b) establishing industry-standard HTS platforms for clinically validated drug targets (kinases, GPCRs, nuclear receptors, ion channels, etc.) in the disease areas of cancer, inflammation, diabetes and infections; (c) creating high quality small-molecule collections based on privileged drug-like scaffolds; (d) building competence and labs for medicinal chemistry; (e) creating expertise base in IND-enabling studies meeting US FDA regulatory standards for clinical proof-of-concept (POC) of experimental drugs; (f) initiating POC trials for clinical validation of botanical drugs based on Indian systems of medicine; (g) strengthening service providing capabilities in pre-clinical and safety pharmacology under GLP guidelines; (h) building tripartite partnerships among the universities, national institutes and global pharmaceutical companies and (i) creating supporting units for intellectual property, competitive intelligence and regulatory affairs. In conclusion, a country as proud and creative as India has an opportunity to discover and develop new life-saving medicines for its needs as well as that of the world.

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