DRUG DISCOVERY

Robert R. Ruffolo, Jr., Frank S. Walsh, and **Giora Z. Feuerstein**
Wyeth Pharmaceuticals, 500 Arcola Road, Collegeville, Pennsylvania 19426, USA

Keywords: Drug Discovery, Translational Medicine, Genetics, Genomics, Biotechnology, Pharmacokinetics, Pharmacodynamics, Biomarkers, Biologicals, Personalized Medicine

Contents

UNESCO – EOLSS SAMPLE CHAPTERS

Summary

Medicines are a fundamental part of human life in all societies and are a cardinal factor in improving human life span, infant survival, general health and enhanced abilities and capacities. Evolving from empiricism, contemporary drug discovery and development is currently a highly scientific, complex and rapidly advancing discipline. Drawing from fundamental basic research conducted in academic, government and pharmaceutical companies across the world, significant improvements in knowledge of human genetics, molecular mechanisms of disease and integrated biological systems functions allow for more rational discovery and design of drugs that are ever more safe, efficacious and innovative.

The scientific advances made since the 1950s, including deciphering the complete human genome as well as many other forms of life, have opened new horizons in designing and engineering superior medicines and diagnostic technologies that allow for more effective treatments of many diseases that were previously thought to be intractable. No better examples can be illustrated than the progress made in the treatment of certain cancers by targeted therapies based on drugs that selectively eliminate cancer cells while sparing normal cells. Likewise, genetically engineered biologicals, such as clot dissolving drugs and tumor necrosis factor (TNF) inhibitors, have redefined the therapies for acute myocardial infarctions and certain autoimmune disorders, such as rheumatoid arthritis, respectively. Moreover, the detailed understanding of the human genetic "blue-print", the expression patterns of genes and their translational products, will provide vast opportunities to discover and develop even more potent, efficacious and safe drugs that have the potential to treat, and possibly even cure, a number of devastating genetic disorders.

The pharmaceutical industry is leading the way in "personalized medicine" which aims to provide more specific therapies to individual patients or limited populations of patients based on individual risks for disease or unique expression profiles of genes or proteins to allow for greater optimization in drug treatment with even greater degrees of safety. The combined scientific and technological achievements that will likely occur as a result of greater collaboration between the pharmaceutical industry, health authorities, academia and government research institutes hold the promise for unprecedented advancements in the diagnosis and treatment of many diseases that have no current therapies, or alternatively will allow existing treatments to be more appropriately individualized to specific patients or patient sub-populations.

1. Introduction

Humans in all societies aspire to enjoy longevity, happiness and a disease-free life span. There are many determinants that impact this goal, such as individual genetics, environmental factors and choices made in lifestyle. Diet no doubt plays a prominent role in our well-being and in some of the major diseases that can afflict certain populations. As susceptibility to disease can relate to the foods we eat, so can some of the medicines that are used to treat human disease. Indeed, some of the first medicines represented bioactive molecules that were derived from natural sources, which were often identified serendipitously. Such natural products have been documented in ancient societies as products used to elicit personal excitations, sensations, hypnosis, physical and reproductive benefits. In fact, the deliberate exploration for therapies derived from natural products marked millennia long "empirical drug discovery".

Over the past 2 centuries science and technology transformed drug discovery into a highly complex scientific process. The emergence of physics and chemistry as discrete scientific disciplines, which were applied to biological systems, has yielded knowledge of the discrete chemical composition of many biologically active natural products (e.g., morphine, digitalis, atropine) and a more detailed understanding of their physico-chemical properties. By natural extension, this has led to rational modification of numerous natural products that have led to new or improved semi-synthetic products and then to fully synthetic products that dominate drug therapy today. Furthermore,

UNESCO – EOLSS SAMPLE CHAPTERS

significant improvements in our understanding of the biological sciences have provided greater insights on organ structure, function and integrity from the macrostructures to the most discrete molecular formations. This in turn has led to greater appreciation of the causes and diagnosis of disease, especially at the molecular level. Today, we often know the site of drug action at the level of the receptor, enzyme, ion channel and structural components. As a result, we are now able to design newer and more innovative drugs that can profoundly change the course of human disease.

The parallel progression of physico-chemical knowledge of drugs and the greater understanding of biological systems has resulted in our ability to design small molecules and biologicals in a rational manner, to manipulate targeted molecules in biological systems to augment or suppress their actions. These achievements are responsible for the "era of rational drug design" that has yielded hundreds of new medicines with major impacts on human health and wellbeing.

Most notable among these new drugs are those that interact with discrete cell surface receptors (especially the G-Protein coupled receptors), which originate signaling pathways that govern discrete cellular functions and ultimately organ responses. The advances made in mitigating devastating diseases such as schizophrenia, depression, heart failure and gastrointestinal disease, to name but a few, by drugs that modulate discrete receptors, have had a tremendous impact on human health and have provided significant societal benefit. Likewise, understanding the physiology and biochemistry of ion channels (Ca^{+2}, Na^{+}, K^{+}, H^{+}, Cl^{-}) has yielded new drugs to treat cardiac arrhythmias, heart disease, hypertension and certain neurological disorders, while altering enzyme function has resulted in new medicines to treat diseases such as atherosclerosis, hypertension, hemophilia and devastating neurodegenerative diseases such as Alzheimer's Disease.

Although the emergence of the "era of rational drug design" has been enormously successful, and is still the main endeavor for future drug discovery in the pharmaceutical industry, a third era appears to be evolving, namely the "era of genomic based therapeutics". The genomic era of drug discovery is based on the complete elucidation of the genetic and genomic "blue print" of humans, and to some extent the understanding, albeit incomplete, of how this genetic blue print relates to human disease. The genomic era of drug discovery provides for the first time the ability to discover and develop drugs that may modify the genetic or genomic blue print of an individual to result in a quantum improvement in our ability to discover new therapies for diseases with high, and currently unmet, medical need. Gene transfer technology may eventually allow for the supplementation or replacement of defective genes on a permanent basis, the treatment of hemophilia by gene transfer of coagulation factors (e.g., actor IX) or treatment of the devastating neurological disease, Huntington's Disease, through insertion of a normal gene. Likewise, engineered ribonucleic acids (RNAs) that have the capacity to silence aberrant transcriptional events (e.g., ribozymes or small interference RNAs) may lead to treatments, or even cures, for metabolic diseases (e.g., diabetes) or the macular degeneration of the retina that leads to blindness.

Most exciting are efforts that may lead to *de novo* engineering of cellular, tissue and organ health that may emanate from the discovery of pleuripotential stem cells

UNESCO – EOLSS SAMPLE CHAPTERS

(embryonic stem cells) that may be engineered to function in a variety of different phenotypes and delivered by design to replace damaged, failed or dysfunctional tissues and organs. In fact, such re-engineered organs could potentially surpass the capabilities and capacities of original organs whose functions are bound by the individual's inherent genetic microenvironment. Most challenging, yet potentially feasible at a technical level at some point in time, may be therapies aimed to modify the very fundamental processes that are associated with ageing.

Pharmaceutical companies, in collaboration with academia, government and health services, are poised at the onset of the 21st century to deliver previously incomprehensible therapeutic opportunities that will allow for unprecedented improvements in human life, treatment of disease improvements in wellbeing and even increases in life expectancy. Most of us hope to live long enough to benefit from these advances.

2. The Modern Drug Discovery Process

The contemporary drug discovery and development process represents complex, diverse, highly regulated and intense team effort. The discovery and development of innovative new medicines is a lengthy process that takes on average 10-15 years from conception of the idea to the availability of the drug to patients. This process requires enormous investments of money and highly skilled human resources that need to be sustained over years, despite the fact that any individual drug discovery and development effort is far more likely to fail than succeed. The high attrition rate that is characteristic of drug discovery and development results in part from the obscurities of disease mechanisms (etiology and progression) that underpin the resulting pathophysiology, as well as insufficient understanding of key fundamentals of human biology. Drug discovery is driven by medical need, as well as the business forces that will provide for reward to compensate for the inordinate risk taken by pharmaceutical companies. The medical need is relatively easy to understand and is derived simply from knowledge of the pathophysiology of diseases that currently afflict the population and the therapeutic voids that exist. The business forces are not well understood by most, but stem from the fact that the financial investment to discover and develop a new drug is high, as are the risks, and in order to foster innovation, those pharmaceutical companies who take such risks need to be compensated sufficiently; not only to pay for costs expended, but also to allow for future investments in new research and technologies. A full understanding of the realities of drug discovery and development is necessary to understand the processes involved in bringing new medicines to patients.

The process of drug discovery in the pharmaceutical research and development (R&D) setting has several logical steps:

2.1. Target Selection

Target selection is typically where the drug discovery process begins. This represents the set of activities that aim to identify a molecular target that is thought to be relevant to the disease pathology and which becomes subject for manipulation by rationally designed small molecules or genetically engineered biological (usually protein) agents.

UNESCO – EOLSS SAMPLE CHAPTERS

The considerations involved in the selection of the most appropriate molecular target for new drug discovery is a highly complex process. First, inasmuch as most human diseases are poorly understood at the molecular level, the selection process is fraught with significant uncertainties, and therefore risk. Evidence on the potential role of a molecular target for drug discovery may, however, be deduced from one or more types of observations:

- Inherent human genetic aberration that increases or decreases a specific molecular function. Such a situation may be exemplified by an abhorrent enzyme activity that occurs in a certain cancer and hence, such an enzyme could become the molecular target for a drug discovery effort directed to that cancer. Likewise, loss of gene function due to an inherited or spontaneous gene mutation, such as coagulation factors VIII or IX, that results in severe bleeding diathesis that is characteristic of hemophilia. Such a defect could be corrected, and potentially cured, by replacement or correction of the specific genetic deficiency.
- Artificially induced genetic manipulation in experimental animals. An advance in the generation of genetically modified animals (primarily mice) allows one to achieve a better insight into the specific functions of genes and their products (proteins) through elimination ("knock-out") of the gene in question. For example, deletion in mice of the gene that produces the enzyme aggrecanase, which breaks down important cartilage matrix, results in resistance to bone and cartilage erosion, a phenomenon that occurs in patients with the highly prevalent joint disease, osteoarthritis. By inference, targeting aggrecanase may result in a new therapy for the treatment of osteoarthritis, and possibly other disorders of joints and bone.
- Differential expression patterns of newly discovered or known genes/proteins either in the human disease itself or in an animal model of human disease can yield extremely valuable information. The specific expression, or lack of expression, of a gene or protein in the cells or organs of human disease can provide strong evidence that such a gene or protein may be a relevant molecular target for initiation of a drug discovery effort. Depending upon the specificity/selectivity of the gene expression, an assessment can often be made of the likelihood for development of more focused therapies with potentially greater safety, and could result in a "targeted therapy".
- Association analysis, using bioinformatics methodologies, of genes, proteins and pathways known to control important cellular events such as proliferation, differentiation, apoptosis and organ formation. Such "*in silico*" methods that can predict the function of genes and/or proteins from their primary amino acid sequences, 3-dimensional shapes, common structural motifs etc, can provide insights years before actual proof-of-concept is established experimentally in animal models.
- The use of natural products or existing drugs as "pharmacological tools" to probe molecular pathways and identify discrete molecular interactions that underpin disease or pathophysiological states.

UNESCO – EOLSS SAMPLE CHAPTERS

-
-
-

TO ACCESS ALL THE **20 PAGES** OF THIS CHAPTER,
Visit: http://www.eolss.net/Eolss-sampleAllChapter.aspx

Bibliography

Chang E. and Harley C.B. (1995). Telomere length and replicative aging in human vascular tissues. *Proc Natl Acad Sci USA* **92**, 11190–11194. [This reference provides insights on potential therapeutics for aging.]

Feuerstein G.Z., Rutkowski J.L., Walsh F.S., Stiles G.L. and Ruffolo R.R. Jr. (2007). The Role of Translational Medicine and Biomarker Research in Drug Discovery and Development. *American Drug Discovery*. In press. [This review provides fundamentals for biomarkers role in drug discovery.]

Haeselden J.N. and Nicholls (2006). Personalized medicine progresses. *Nature Medicine* **12**, 510-511. [This reference provides insights on personalized medicine.]

Jain K.K. (2006). A critical review of the Royal Society's report on personalized medicine. *Drug Discovery Today* **11**(13/14), 573-579. [This review provides perspective from the British Royal Society regarding personalized medicine.]

Lamb J., Crawford E.D., Peck D., Modell J.W., Blat I.C., Wrobel M.J., Lerner J., Brunet J-P., Subramanian A., Ross K.N., Reich M., Hieronymus H., Wei G., Armstrong S.A., Haggarty S.J., Clemons P.A., Wei R., Carr S.A., Lander E.S. and Golub T.R. (2006). The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease. **Science 313**, 1929-1934. [This reference emphasizes the opportunities and issues in genomics based medicine.]

Okie S. (2005). What ails the FDA. New England Journal Medicine **352**(11), 10631066.

[This reference provide regulatory perspective in drug discovery.]

Office of Inspector General (2005). FDA's review process for new drug applications: a management review. www.oig.hhs.gov/oei/reports/oei-01-01-00590.pdf . [This web site provides comprehensive material on regulatory issues in drug discovery.]

Phillips K.A., van Bebber S. and Issa A.M. (2006). Diagnostics and biomarker development: priming the pipeline. *Nature Review* 5, 463-469. [This reference provides perspectives on biomarkers, diagnostics and prognostic part of drug discovery.]

Perel P., Roberts I., Sena E., Wheble P., Briscoe C., Sandercock P., Macleod M., Mignini L.E., Jayaram P. and Khan K.S. (2006). Comparison of treatment effects between animal experiments and clinical trials: systematic review. *British Medical Journal* **334**, 197-203. [This review expands on the role of animal models in drug discovery.]

Potti A., Dressman H.K., Bild A., Riedel R.F., Chan G., Sayer R., Cragun J., Cottrill H., Kelley M.J., Petersen R., Harpole D., Marks J., Berchuck A., Ginsburg G.S., Febbo1 P., Lancaster J. and Nevins J.R. (2006). Genomic signatures to guide the use of chemotherapeutics. *Nature Medicine* **12,** 1294-1300. [This review provides insights on genomics and pharmacogenetics in drug discovery.]

Sams-Dodd F. (2006). Strategies to optimize the validity of disease models in the drug discovery process. *Drug Discovery Today* **11**(7/8), 355-362. [This reference describes issues in animal models in drug discovery.]

UNESCO – EOLSS SAMPLE CHAPTERS

Biographical Sketches

Robert R. Ruffolo, Jr., Ph.D, DSc.
Dr. Ruffolo is President of Research & Development for Wyeth Pharmaceuticals, and corporate Senior Vice President of Wyeth. He joined Wyeth in 2000 as Executive Vice President, responsible for Pharmaceutical Research and Development. Prior to joining Wyeth, Dr. Ruffolo spent 17 years at SmithKline Beecham Pharmaceuticals where he was Senior Vice President and Director of Biological Sciences, Worldwide. Before joining SmithKline Beecham, Dr. Ruffolo spent 6 years at Lilly Research Laboratories.

During his career in the Pharmaceutical Industry, Dr. Ruffolo played a significant role in the discovery and/or development of a number of marketed products, including carvedilol (Coreg/Kredex/Dilatrend) for the treatment of congestive heart failure and hypertension, ropinerole (Requip) for Parkinson's Disease, dobutamine (Dobutrex) for congestive heart failure and eprosartan (Teveten) for hypertension.

Dr. Ruffolo received his B.S. degree in Pharmacy *summa cum laude with Distinction* in 1973, and his Ph.D. degree in Pharmacology in 1976, both from The Ohio State University. Thereafter, he spent two years as a postdoctoral fellow at the National Institutes of Health. Dr. Ruffolo has authored nearly 500 full-length publications and over 200 abstracts, and has edited 17 books. He is the Editor-in-Chief of *Current Opinions in Pharmacology*, and was the Editor-in-Chief and Founder of both *Pharmacology Reviews and Communications* and *Pharmacology Communications*. Dr. Ruffolo has served on the editorial boards of 28 international scientific journals.

Dr. Ruffolo has received a number of prestigious awards, including *Chief Scientific Officer of the Year* (2004), *George B. Koelle Award for Scientific Excellence (2005), Lorenzini Gold Medal for Biomedical Research* (1999), *John Jacob Abel Award in Pharmacology* (1988), *Centennial Award for Drug Discovery* (2006), *Prix Galien Special Commendation for Excellence and Innovation in Research* (1996), and the *Distinguished Alumni Award* from The Ohio State University (1989). In 1997, Dr. Ruffolo was honored by SmithKline Beecham for his pioneering research on carvedilol (Coreg/Kredex), which radically changed the treatment of congestive heart failure and has since become the standard of care for this debilitating disease. In 2004, the American Chemical Society recognized Dr. Ruffolo for Leadership in creating a research environment that promoted innovation, which led to the *Heroes of Chemistry Award* presented to Wyeth researchers. In 2005, *R&D Directions* recognized Dr. Ruffolo twice for the transformation of Wyeth's Research & Development organization and its drug development pipeline, first with the *Top Ten Pipelines Award,* in which they designated Wyeth as *"The Pipeline To Watch"*, and second for being *"Industry Best"* with respect to the number of drugs in their list of top *"100 Great Investigational Drugs*". In 2006, *R&D Directions* recognized Dr. Ruffolo again for Wyeth's drug development pipeline, which was once more designated as a *Top Ten Pipeline* and selected as the *"Strongest Primary Care Pipeline"*. PharmaVOICE identified Dr. Ruffolo as one of the *100 Most Inspiring People in the Life-Sciences Industry*, the organization, Pharmer, listed Dr. Ruffolo among the 200 most *Distinguished Pharmaceutical Scientists* in the world and Med Ad News identified him as a *Rising Star* in the Pharmaceutical Industry. Recently, the American Society for Information Science & Technology designated Dr. Ruffolo as a *Highly Cited Scientist* for being among the top one-hundred most cited Pharmacologists in the world over the past two decades. In February of 2006, Dr. Ruffolo was profiled in *BusinessWeek Magazine* for his role in re-engineering R&D at Wyeth, and most recently, Dr. Ruffolo was awarded an Honorary Doctorate of Science degree from West Virginia University, and also served as Commencement Speaker for the School of Medicine at the 138th Commencement of West Virginia University.

Frank Walsh received his Ph.D. in Biochemistry from University College, London, in 1977. He then undertook a one-year post doctoral research fellowship at the National Institute of Health (NIH) in Bethesda, Maryland, USA, returning to the UK in 1979 to the Institute of Neurology in London. In 1989, Frank moved to the United Medical and Dental Schools of Guy's and St. Thomas's Hospitals (UMDS), London, becoming the Sir William Dunn Professor of Experimental Pathology, and later served as the UMDS's Research Dean.

In 1997, Frank moved to SmithKline Beecham (SB) Pharmaceuticals at Harlow, UK, to become Vice President and Director of Neuroscience Research. With the creation of GSK from the merger of SB and GW, Frank became Senior Vice President and Head of the Company's Neurology-CEDD.

UNESCO – EOLSS SAMPLE CHAPTERS

In 2002, Frank moved to Wyeth Research, Collegeville, Pennsylvania, USA, to become Senior Vice President and Head of Discovery Research. In January, 2005, Frank was promoted to Executive Vice President, Discovery Research Worldwide.

Frank serves on a number of advisory boards including those of the UK Medical Research Council's Centre for Developmental Neurobiology; the ALS Research Center at Johns Hopkins University, Baltimore, USA; the UK Muscular Dystrophy Campaign; and the CEO Council of the New York Academy of Sciences. He holds Visiting Professorships at London University's King's College, the University College Dublin, and was elected to the Academy of Medical Sciences (London) in 2003. In October of 2004, Frank was awarded an Honorary Degree "Laurea Honoris Causa," in Chemistry and Technology of Drugs from the University of Perugia, Italy. In addition, in October of 2006, Frank was awarded the Honorary Doctorate "Laurea Honoris Causa" in Pharmacy from the University of Bologna, Italy. Also of note, Frank received the "USA-Ireland Life Science Award" from BioLink during their meeting in early 2006. Frank is currently Chief Editor of the journal, *Molecular and Cellular Neuroscience*.

Giora Z. Feuerstein, MD, MSc., F.A.H.A.

Giora Feuerstein joined Wyeth in 2005 as the Senior Director, Translational Medicine.

Before joining Wyeth, Giora maintained Directorship positions in discovery of cardiovascular, stroke and metabolic disease programs for 16 years in other pharmaceutical houses. At SmithKline Beecham (1980-1998), Giora served as the Director of the Department of Cardiovascular Pharmacology where he led the Carvedilol (COREG) program, which became the first beta-blocker launched for treatment of chronic heart failure. In addition, Giora was associated with the discovery and development of eprosartan, enrasartan, lotrafiban and several other compounds for diverse cardiovascular indications, including stroke and anti-arrhythmic drugs.

In 1998, Giora joined DuPont Pharmaceuticals as the head of the Cardiovascular Disease Department leading thrombosis, cardiovascular and metabolic syndrome programs. Razaxaban, a lead FXa inhibitor, was advanced to phase II development prior to acquisition of the DPC by BMS. In 2003, Giora joined Merck Co, Inc, West Point as the Executive Director, Cardiovascular Diseases, where he established a new department leading efforts in hypertension (renin inhibitors), metabolic syndrome and cardiac arrhythmias. In addition, Giora was appointed as member of strategic forums in cardiovascular drug development and chaired licensing and business development committees.

Prior to joining the pharmaceutical industry, Giora held the position of Professor (Research) in the USUHS, Bethesda, MD (1981-1988), where he was the Director of the Neurobiology Research Laboratories, heading research in central and peripheral regulation of the cardiovascular system, with a focus on adrenergic and peptidergic systems. In addition, Giora developed research lines in stroke, gene expression and pharmacological strategies.

Giora received his MSc degree in Pharmacology from the Hebrew University, Jerusalem, Israel in 1970 and his MD degree from the Hadassah Medical School, Jerusalem Israel. Following a lectureship position in the department of Pharmacology, Hadassah Medical School (1976-1979), Giora obtained the Fulbright scholarship for further training at the National Institute of Health (NIH) Bethesda, MD (1979-1981) in the Laboratory of Clinical Sciences (Chief, I Kopin) focusing on sympathetic nervous system control of the cardiovascular system.

Giora holds an adjunct position in two academic organizations (Med College of Georgia, Augusta GA and Jefferson Medical College, Philadelphia,PA). He also serves on editorial boards of the J Pharmacology Experiment Therapeutics; Biochemical Pharmacology, J Cerebral Blood Flow Metabolism, Circulation Research, Stroke. Giora is the recipient of several national and international awards, including the Award of Excellence in Cardiovascular Research, AHA, 1987; Prix Galien Award for Drug Discovery (endothelin antagonist) 1994; and the Conrad R Lam Award for Cardiovascular Research, Henry Ford Foundation, 2001.

Giora has authored and coauthored over 650 publications, of which over 400 are in peer review journals. He is also co-inventor on 12 patents and has edited 8 books.

UNESCO – EOLSS SAMPLE CHAPTERS