Discovery of Innovative Therapeutics: The Pharma Perspective

Magid Abou-Gharbia

Wyeth Research, Chemical & Screening Sciences, 500 Arcola Road, Collegeville, PA 19426, USA; E-mail: abougam@wyeth.com

Drug Discovery and Development is a challenging and complex process that involves the dedicated efforts of many mulidisplinary R&D functions. Compared to the past, today's innovative drug discovery has become more costly and time-consuming, with fewer novel therapeutics making it to market. Small molecules have been historically the cornerstone of the pharmaceutical industry providing it with stability and sustained growth. The advent of the biotech revolution that began with the pioneering recombinant work of the 1970's, and the successful commercialization of protein-based therapies have introduced a new dimension for discovering innovative therapeutics. Accordingly, today's discovered and marketed drugs fall into three pharmaceutical platforms small molecules, proteins and vaccines.

Breakthroughs in innovation and process refinements have dominated drug discovery during the last decade, which have aimed at increasing efficiencies by reducing cycle time and increasing success rate throughout all phases of R&D. Several medicinal chemistry approaches are being utilized successfully to optimize initial leads identified via screening of natural product and small molecule libraries or by rational drug design. In particular, advances in technology have spurred renewed interest in natural products-based drug discovery. Precise synthetic methods and high-resolution analytical tools now enable chemists to perform targeted modification of complex natural products. Genetic engineering of biosynthetic pathways of proven natural product scaffolds can provide new starting points for optimization of these privileged structures. Multi-dimensional lead optimization is now an essential component of all lead optimization strategies, since the critical path activities have become broader and requirements for compound advancement more rigorous.

The lecture will give an overview of the drug discovery and development process, illustrating its evolution over past decades, impact of enabling technologies in discovering innovative therapeutics as well as highlighting attributes of Wyeth recently discovered drugs.

Current Drugs for the Treatment of HIV Infection (AIDS): Role of Acyclic Nucleoside Phosphonates

Erik De Clercq

Rega Institute for Medical Research, K.U.Leuven, B-3000 Leuven, Belgium

There are presently twenty-four antiretroviral agents which have been formally approved for the treatment of human immunodeficiency virus (HIV) infection (AIDS): (i) seven nucleoside reverse transcriptase inhibitors (NRTIs): zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine, (ii) one nucleotide reverse transcriptase inhibitor (NtRTI): tenofovir disoproxil fumarate (TDF); (iii) three non-nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine, delavirdine, efavirenz; (iv) ten protease inhibitors: saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir, tipranavir, darunavir; (v) one fusion inhibitor (FI): enfuvirtide; (vi) one co-receptor inhibitor (CRI): maraviroc; and (vii) one integrase inhibitor (INI): raltegravir. All of these compounds, except for enfuvirtide (which has to be injected subcutaneously), are orally available, and are generally administered in multiple drug combination regimens, so as to achieve synergistic activity with reduced likelihood for drug resistance development. One such drug combination, containing the acyclic nucleoside phosphonate TDF together with emtricitabine and efavirenz, has been formulated as an oral pill to be taken once daily. Cornerstone in this combination is TDF, which, in addition to its activity against HIV, is also effective against hepatitis B virus (HBV) infection. At present, three nucleoside analogues (lamivudine, entecavir and telbivudine), and one acyclic nucleoside phosphonate, adefovir dipivoxil, besides (pegylated) interferon, have been approved for the treatment of HBV infection. In addition to tenofovir and adefovir, cidofovir is the third acyclic nucleoside phosphonate registered for clinical use, i.e. against cytomegalovirus retinitis in AIDS patients; cidofovir has also proven effective in the treatment of herpes-, papilloma-, polyoma-, adeno-, and poxvirus infections, as demonstrated particularly in immunosuppressed (i.e. AIDS) patients.

The Challenges of Implementing Biomarkers in Clinical Trials

Stephen T. Furlong

(Discovery Medicine, AstraZeneca Pharmaceuticals, DE, USA), 1406 Shipley Road, Wilmington, DE 19803, 302-764-6922(H) - 302-886-8588 (W) 302-898-7207(M); E-mail: stephen.furlong@astrazeneca.com

This is an exciting time for discovery and development of biomarkers. However, there are also many challenges and obstacles that could slow the acceptance of new biomarkers. In this lecture we will review the different types of biomarkers and look at some of the different types of platforms for new biomarker discovery. We will also compare biomarkers from different disease areas and consider specific examples of how the use of biomarkers is changing the design and conduct of clinical trials. In particular, we will look at the use of biomarkers for safety monitoring, using hepatotoxicity and nephrotoxicity as examples. To further illustrate how the field is evolving, we will compare the use of single biomarkers to multiplex panels and consider the advantages and disadvantages of multiplex panels. Finally, we will discuss the qualification process for biomarkers, the various consortia and initiatives that have been undertaken to speed both biomarker discovery and qualification, and the role of the regulatory agencies in this process.

Inflammation and Allergy Drug Design and Discovery

Kenji Izuhara

Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School, 5-1-1, Nabeshima, Saga, 849-8501, Japan; Tel: +81-952-34-2261; Fax: +81-952-34-2058; E-mail: kizuhara@med.saga-u.ac.jp

The incidence of allergic diseases, including bronchial asthma, atopic dermatitis, and allergic rhinitis, has dramatically increased in recent decades, especially in urban and industrialized areas. Various agents against allergic diseases are now available, and show significant effects. However, there still exist several problems in the present treatments; side effects, unresponsive patients, and unnecessary administration of agents. Therefore, it is medically and socially important to develop an agent targeting a molecule correlated with the pathogenesis of allergic diseases and administers such an agent based on the pathogenesis of each patient. Allergic diseases are complex disorders in which a lot of cells and mediators are involved. Various attempts to improve or cure allergic diseases targeting particular cells or mediators are now underway. In this session, several trials to find mediators involved in the pathogenesis of allergic diseases and to develop agents targeting such mediators will be presented.

BACE Inhibitors for the Treatment of Alzheimer's Disease

Allen B. Reitz

International Drug Discovery Institute, Lansdale, PA 19446, USA. Telephone: +1-215-628-5615; Fax: +1-215-628-4985; E-mail: areitz@i-ddi.org

The search for new and useful therapeutic agents directed to treat disorders affecting the Central Nervous System (CNS) comprises a major portion of drug discovery research throughout the world, generally divided into the areas of psychiatry and neurology. Alzheimer's Disease (AD) is the most prevalent neurological disorder, currently afflicting 26 million people. In addition, the incidence of AD is growing with the increasing population of the elderly. The amyloid hypothesis has been proposed to explain the etiology of AD; β-secretase (BACE) and γ-secretase cleave the amyloid precursor protein (APP) at the N- and C-terminus, respectively, to provide the β-amyloid peptides, $A\beta_{1-40}$ and $A\beta_{1-42}$, which aggregate into neurotoxic oligomers and fibrils. The inhibition of BACE promises to be a disease-modifying approach to treat AD. We initiated a program to discover and design novel BACE inhibitors starting with a high throughput screen of the Johnson & Johnson Pharmaceutical Research and Development corporate compound collection. From this exercise, several low micromolar inhibitors of BACE were identified. The most promising hit was JNJ-715754 (Ki = 1 uM), for which a co-crystal structure was obtained in the active site of the aspartic protease BACE. The X-ray structure of JNJ-715754 in BACE was used to guide the design of more potent inhibitors, and the best have Ki's in the nanomolar range. In addition, 17 other X-ray structures of various analogs in BACE were solved providing further insight to empower continued synthesis. A large library (>1,200) of related chemical derivatives was prepared involving substantial structural variation such as heterocyclic replacement, macrocyclization, and modulation of ADME parameters such as pKa, log P, and MW. The overall program will be discussed in detail, including *in vivo* evaluation of several of the analogs prepared.