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Letter from Editor



Dear friends and colleagues,

In the past 18 months or so, the pharmaceutical industry has undergone significant restructuring and many colleagues are being affected. Among the biggest events, the acquisition of Pfizer-Wyeth, Merck Schering-Plough deals topped the news. These changes were implemented right before the storm--the global financial crisis and will likely to continue across the industry. What prompted these re-structurings are the fundamental problems in the industry in the past few decades—high attrition, low productivity, long cycle time, tougher FDA approval, among others. Although there is no quick fix for these issues, big companies are adopting new strategies aiming to boost productivity

and shorten cycle times in order to bring drugs to the market as soon as possible. Among these new initiatives, portfolio re-balancing is the first step to achieve the goal.

The key therapeutic areas after the re-balancing are generally comprised of Oncology, Neuroscience, Inflammation, and Biopharm. These are the areas that provide promise in meeting the patient needs. In terms of target class, kinases represent more than 1/3 of the targets in drug discovery piechart. These enzymes are very important elements of the cellular signal-transduction in Oncology, Inflammation and other therapeutic areas. Recent approvals of small molecular drugs targeting kinases make these enzymes second largest target class after GPCRs in drug discovery pipeline. HTS campaign provides a common method that would sieve through thousands of thousands synthetic compounds in order to provide a starting point for lead molecule. The focus of each of drug discovery phase determines the need of a particular format for kinases. Normally, biochemical assay is employed in primary HTS. Cell-based assay is used as a secondary assay to follow up confirmed hits. Although existing assay formats are of abundance, novel assays are still in high demand. This demand comes from the need for better sensitivity or biological relevance. An assay that can be used in primary screening as well as mode of action (MOA) studies is preferred to carry on the continuity. At the same time, companies are conscious about cost. In order to screening more compounds with flat budget, the cost per well has to be reduced significantly.

In this issue of TBI, we invited a few experts working in the kinase drug discovery field to review novel assay technologies in this particular area and provide their personal opinions about the strengths and weaknesses of each assay technology. There are three chapters in the issue. In the first chapter, Dr. Li gave a brief review of biochemical assays employed in the lead discovery. The assays were divided into three groups: phosphopeptide detection, ATP depletion and ADP production. In each group, typical assay formats were presented based on detection technology. The author summarizes the pros and cons of each assay and their typical applications, whether it is for HTS, profiling, or MOA studies. This summary will be of value to users in selecting kinase assays for their research needs. In the second chapter, Dr. Xian reviewed cell-based assay strategies for kinase inhibitor discovery. The technologies were divided into two categories: antibody-based and antibody-free. In each category, the assays were divided further by either using regular cell line or engineered cell line. At the end of the chapter, the author touched upon label free detections. This review is quite comprehensive—covers more frequently used methods in the field. The summary table outlines the virtue of each assay, which provides a useful guideline for users. In chapter 3, Dr. Wu expanded on the label-free detection methodologies.

It is my hope that these reviews will familiarize readers with these technologies and make it easier for scientists in this field to select fit-for-purpose assays in their drug discovery effort.

Hu Li, Ph.D.

Editor

Facts Behind Novel A(H1N1) Pandemic Panic

The unexpected surge of nearly pandemic A(H1N1) flu has brought the whole world to the highest alert since SARS. Although the new virus later was shown to be much milder than anticipated with mortality rate close to or slightly higher than that of regular flu virus. However, if the 1918 flu pandemics taught us anything, we should be fully prepared for a possible “second wave” later in the year.

Scientists in the world are racing to find out more about the virus to prepare new arsenals to fight the new strain and to prevent a possible catastrophe in the near future. The following information is assembled from several public sources, mainly from the U.S. Centers for Disease Control and Prevention (CDC). Readers are encouraged to check A(H1N1) related sources for further and timely information.

Genomic Makeup

On May 16th, 2009, the National Microbiology Laboratory in Winnipeg, Manitoba became the first lab to have completed the genomic mapping of the new A(H1N1) virus. The novel A(H1N1) influenza virus is found to be made up of genetic elements from four different flu viruses – North American Mexican influenza, North American avian influenza, human influenza, and swine influenza virus that is typically found in Asia and Europe. Preliminary genetic characterization found that the hemagglutinin (HA) gene was similar to that of swine flu viruses present in U.S. pigs since 1999, but the neuraminidase (NA) and matrix protein (M) genes resembled versions present in European swine flu isolates. It is believed that virus of swine origin has been evolving for quite some times before it eventually jumped into human and became contagious among people.

Transmission and Syndrome

Limited data available indicate that this virus is transmitted in ways similar to other influenza viruses. Seasonal human influenza viruses are thought to spread from person to person primarily through large-particle respiratory droplet transmission (e.g., when an infected person coughs or sneezes near a susceptible person). Transmission via large-particle droplets requires close contact between source and recipient persons because droplets do not remain suspended in the air and generally travel only a short distance (< 6 feet). Contact with contaminated surfaces is another possible source of transmission and transmission via droplet nuclei (also called “airborne” transmission). Because data on the transmission of novel H1N1 viruses are limited, the potential for ocular, conjunctival, or gastrointestinal infection is unknown. Since this is a novel influenza A virus in humans, transmission from infected persons to close contacts might be common. All respiratory secretions and bodily fluids (**diarrheal stool**) of novel influenza A (H1N1) cases should be considered potentially infectious. The estimated incubation period is unknown and could range from 1 to 7 days, and more likely from 1 to 4 days.

People infected with A(H1N1) virus showed clinical syndromes ranging from mild respiratory illness, to lower respiratory tract illness, dehydration, or pneumonia. Other manifested complications, similar to seasonal influenza, include exacerbation of underlying chronic medical conditions, upper respiratory tract disease (sinusitis, otitis media, croup) lower respiratory tract disease (pneumonia, bronchiolitis, status asthmaticus), cardiac (myocarditis, pericarditis), musculoskeletal (myositis, rhabdomyolysis), neurologic (acute and post-infectious encephalopathy, encephalitis, febrile seizures, status epilepticus), toxic shock syndrome, and secondary bacterial pneumonia with or without sepsis.

Diagnosis

The U.S. Centers for Disease Control and Prevention (CDC) has issued guidelines for Diagnosis