Advanced Product Development for Multiplex Infectious Disease Diagnostics
Summary of a NIAID Workshop held on June 27, 2005

Challenges to Be Addressed

A majority of clinical diagnostic tests and technologies for infectious diseases offer only a single diagnosis per test. For most patients, the clinician must order a series of diagnostic tests to assist in identifying the disease-causing pathogen. There is an urgent need to develop **multiplex diagnostic instruments** – products capable of rapidly processing and screening a patient's sample to identify a collection of bacterial and viral pathogens.

NIAID recognizes the urgent need for rapid, highly sensitive and specific clinical diagnostics that are easy to use, cost-effective, and can diagnose individuals infected with pathogens or exposed to toxins. The ability to diagnose pre-symptomatic, symptomatic, or non-specific symptomatic individuals is essential for public health laboratories, hospital-based clinical laboratories, and point-of-care settings so that appropriate therapy can be initiated. Medical diagnostics that will rapidly distinguish whether an individual is infected by a biological threat agent or a common pathogen that causes similar symptoms are of high priority, as are diagnostic tools to determine drug sensitivities and simultaneously detect a broad range of infectious agents in clinical specimens.

Purpose of Workshop

The purpose of this workshop was to inform NIAID about the current status of multiplex infectious disease diagnostics, determine criteria to assess performance of multiplex instruments, and identify current and potential obstacles to developing and integrating this functionality into the clinical setting.

Participants

Workshop participants included NIAID staff as well as representatives from industry, clinical microbiology laboratories, academic research laboratories, non-profit organizations, Department of Homeland Security, Centers for Disease Control and Prevention, Food and Drug Administration, the Department of Defense including the Defense Advanced Research Projects Administration, and the Bill and Melinda Gates Foundation.

NIAID's Mission and Role

NIAID supports basic and applied peer-reviewed research to prevent, diagnose, and treat infectious and immune-mediated illness. The Institute supports emerging technologies and early and late stage product development of medical diagnostics through grants and contracts. To develop improved diagnostics for infectious diseases, NIAID partners with industry, other federal agencies, non-profit organizations, and academic institutions.

Topics Covered

Platform Requirements

The one-day meeting began with an overview and short presentations on diverse technologies being used to develop multiplex infectious disease diagnostic platforms. All of the platforms attempt to provide actionable and timely information for the clinician

that will impact therapeutic decisions for patients with symptoms suggestive of an infectious disease. Designing such tests requires understanding the infection growth rate and process for each pathogen, and demonstrating the availability of each analyte target intended to be used to detect the pathogen.

For example, in some viral infections, by the time the patient presents to a clinician with symptoms there is a minimal amount of virus present in the blood. This limits the usefulness of nucleic acid and antigen detection tests for blood samples in a symptomatic person. In a pre-symptomatic person, however, both nucleic acid and antigen tests may be useful to detect viral pathogens in blood.

Multiplex diagnostic instruments will ideally have orthogonal functionalities and consequently be capable of detecting multiple independent biomarkers for each pathogen. This includes specific pathogen, antibiotic resistance, and host response markers. This expanded capacity would strengthen the diagnostic result that the patient is infected with a particular pathogen, and the clinician could more confidently factor this information into clinical management.

Proposed Multiplexing Strategies

Participants presented strategies for combining analyte targets into a multiplex diagnostic test. One strategy involves a syndrome panel test approach that will combine analyte targets for multiple pathogens known to cause a particular collection of symptoms, e.g. pneumonia, diarrhea, or flu-like symptoms.

The strategy involves screening for a predefined collection of pathogens known to cause a particular set of symptoms. It does not require a detailed understanding of regional or national epidemiological data for the syndrome in question and may be able to identify a patient infected with a rare disease-causing pathogen based on the syndrome.

An alternative strategy is to combine analyte targets into a multiplex test based on possible therapeutic regimens currently being used for a particular collection of symptoms. This approach would require understanding the decision process physicians use to prescribe a therapeutic regimen for a particular collection of symptoms and designing a combination of analyte targets that will test for the presence or absence of pathogens (e.g. antibiotic resistant pathogens) and will guide therapeutic decisions.

This strategy would most likely incorporate epidemiological information and requires knowledge of the specific pathogens a physician would like to identify or eliminate from consideration before prescribing a treatment course for a patient with a particular collection of symptoms. Physicians may be more inclined to accept and incorporate results from this approach into their therapeutic decision making process.

A third approach does not require any information or bias with regard to the disease-causing pathogen and analyzes several targets on a universal component (e.g. rRNA). This method identifies the pathogen based on a combination of targets found in the

pathogen. It would require developing confirmatory tests for novel or unknown pathogens that are identified by this method.

Product Requirements

All participants emphasized that the multiplex system must lead to a marketable product. One of the many criteria considered by industry when developing products is the average number of diagnostic tests requested by clinicians per year. A sufficient number of diagnostic tests must be requested by clinicians in order to justify a company's research and development costs. Researchers in infectious disease diagnostics should consider formulating a strategy to determine whether multiplex diagnostics will lead to better therapeutic decisions, improve a patient's outcome, and reduce health care costs, e.g. by reducing hospital stays or shortening courses of antibiotics. Demonstrating that improved infectious disease diagnoses have a positive impact on public health may stimulate industry interest in developing and marketing new technologies and their associated diagnostic tests.

A multiplex diagnostic system should be an automated comprehensive system capable of isolating the target analyte (such as a nucleic acid or antigen), performing the test, and displaying the interpretation of the multiplex test result. One of the main obstacles in developing some multiplex systems is the difficulty in developing universal, rapid, and efficient clinical sample processing methods.

Participants discussed the minimum technical requirements (e.g. power required, number of biological agents simultaneously detected per test, clinical sample volume, training required) for a multiplex diagnostic instrument. These must be tailored for the intended end-users and their setting. Potential settings include the clinical diagnostics laboratory (hospital or reference), point-of-care testing at the patient's bedside or a physician's office, a battlefield location, or the first-response to a civilian outbreak. Because infectious disease specialists in these settings have a range of microbiological and technological expertise, multiplex platforms must be designed to meet the requirements of personnel in each particular setting. All of the platforms should be affordable for the end user, have low cost per test, provide results within a reasonable interval, and have sensitivity and specificity levels that are equivalent to or better than current gold-standard tests for each pathogen. All will require FDA approval. Additionally it will be necessary to formulate strategies to address annual proficiency testing requirements.

Representatives from the FDA participated in the workshop and presented an overview of the FDA review process for multiplex test systems. The FDA will assess safety to determine that the probable health benefits of using the multiplex diagnostic system will outweigh any probable risks. Additionally, the FDA must determine that the multiplex diagnostic system will provide clinically significant results under intended use and conditions of use. Last March the FDA released the Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems (http://www.fda.gov/cdrh/oivd/guidance/1546.pdf) to provide companies with general recommendations for classification of multiplex test systems as class II devices.

Recommendations

- The infectious disease diagnostics community should consider formulating a strategy to determine whether information obtained from multiplex diagnostics instruments will lead to better therapeutic decisions, improve a patient's outcome, and reduce health care costs, e.g., by reducing hospital stays or shortening courses of antibiotics.

- Improved clinical sample processing methods should be developed.

- Minimum technical requirements for a multiplex diagnostic instrument must be tailored for the intended end-users and their setting.

- A multiplex diagnostic system should be an automated comprehensive system capable of isolating the target analyte (nucleic acid, antigen, etc.), performing the test, and displaying the interpretation of the multiplex test result.

- Multiplex diagnostic systems will ideally have orthogonal functionalities and consequently be capable of detecting multiple independent biomarkers for each pathogen, including specific pathogen markers, antibiotic resistance markers, and host response markers.

- Continue development of partnerships between NIAID, industry, other federal agencies, non-profit organizations, and academic institutions to stimulate development of multiplex infectious disease diagnostics.

- Agencies of the federal government should strive for better coordination of research programs and efforts to develop multiplex diagnostics for infectious diseases.