EVALUATING NEW ANTIVIRAL AND ANTIBIOTIC DRUG CANDIDATES
Advancing your journey from discovery to post-marketing
The development of anti-infective treatments to combat illnesses caused by viral and microbial agents has witnessed many unique advances, most notably in the fights against bacterial infections, hepatitis and HIV. The momentum in this exciting area continues with new tools and methods to better support the development journey. From improved microbial identification to quantitative technological platforms, let’s explore emerging opportunities to develop assays, interpret results and improve clinical trials.

Learn how novel technologies and analytical techniques are accelerating discoveries and transforming results in infectious disease drug development.

Diagnostic and confirmatory screening • Molecular typing assays • Viral load monitoring • Drug and neutralizing antibody resistance testing • Characterization of host biomarkers • Indicators of disease status • Bacterial culture and isolation • Susceptibility testing • Bacterial identification
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PHENOTYPING AND SEQUENCING:
Two Different yet Complementary Methodologies for Measuring Drug Resistance

MAKING SENSE OF PHENOSENSE®

Cell-based infectivity assays, often referred to as phenotypic assays, provide direct quantitative measurements of drug susceptibility that can define resistance for new drugs and drug classes and also identify novel drug-resistance pathways. When trials involve newer drugs or drug classes, cell-based phenotypic assays can be very effective at identifying these active agents.

One type of cell-based drug susceptibility assay is the PhenoSense platform, which utilizes a complement of viral expression vectors to generate pseudovirions that express patient-derived viral sequences and a luciferase reporter that measures infectivity. The particular patient-derived sequences are incorporated into the PhenoSense assay based on the drug target of interest and may include viral, structural and nonstructural proteins.

See diagram on next page
The PhenoSense assay can also be adapted to assess neutralizing antibody responses to a wide variety of envelope viruses including highly pathogenic and transmissible strains. Monogram Biosciences, a member of the LabCorp Specialty Testing Group, provides diagnostic testing services for clients of both LabCorp Diagnostics and Covance, and can even use PhenoSense to assess neutralizing antibody responses to Ebola virus.
THE POWER OF NEXT GENERATION SEQUENCING IN GENOTYPIC ASSAYS

Nucleic acid sequencing-based assays, also called genotypic assays, provide a rapid and broadly accessible prediction of drug susceptibility once drug-resistance profiles are better understood. These assays are often employed when clinical studies involve established drugs with well-defined resistance profiles.

The HIV GenoSure Archive℠ assay is a representative example of the genotypic resistance testing process where the assay is performed by isolating nucleic acid from a sample, in this case, whole blood or PBMCs. The viral drug target sequence of interest is amplified and the DNA sequences are generated using either conventional Sanger or next generation sequencing platforms. A proprietary analysis pipeline analyzes and interprets sequences and test results are then communicated in easily interpretable reporting formats.

See diagram on next page
GenoSure Assay Methodology:
GenoSure Archive Assay as an Example

Next generation sequencing can also support assays for HIV, hepatitis B, C and D, as well as various respiratory viruses along with herpes and hemorrhagic viruses.
THE ROLE OF DRUG-RESISTANCE TESTING TO EVALUATE NEW DRUG CANDIDATES

Identifying appropriate patient populations is a key element to successful enrollment in clinical trials. Even optimizing the background treatment in the placebo arms of a trial can result in a 1-log reduction of viral load in a highly experienced patient population.

▶ Characterizing Resistance Pathways
The selective outgrowth of either minor variants that preexist prior to treatment—or new variants that emerge during treatment—may result in treatment failure, stressing the need for accurate characterization.

▶ Defining Clinical Cut-Offs
An important facet of defining and characterizing drug resistance is the direct demonstration of reduction in drug susceptibility by a resistance-associated mutation. The ability to accurately predict therapeutic activity requires the identification of susceptibility cutoffs that are correlated with treatment outcome. Prior to the availability of clinical response data, the interpretation of antiviral drug-resistance assays is typically assessed using biological cutoffs and then can be compared with the resistance-associated mutation profiles to generate predictive algorithms and help drive more accurate predictions.
The combined forces of Covance and LabCorp now provide Covance clients with access to one of the world’s largest repositories of diagnostic assay test results. These data can be queried to understand cross-sectional and longitudinal profiles of viral and host factor test results. Querying the results of routine tests can also be used to accurately survey the prevalence of naturally occurring substitutions that may impact treatment response.
APPLYING NEW TECHNOLOGIES TO MODERN INFECTIOUS DISEASE TRIALS

MALDI-TOF and molecular technologies like 16S sequencing play an increasing role in accurate identification.

The gradual shift from phenotypic identification platforms to the use of molecular identification platforms has enabled more accurate and precise results, as well as decreased labor cost and reduced testing time.

- MALDI-TOF technology enables identification of more than 95% of the bacteria that are seen at the species level, a level of accuracy that reduces the overall time to results. If required, the identification database can be customized to include genetically engineered bacterial strains.

- 16S sequencing is an advanced genotypic ID systems that can also provide confirmation if MALDI-TOF identification isn't sufficient. It is particularly important in the case of bacteria with unusual phenotypic profiles, rare bacteria as well as slow-growing bacteria. Along with an internal database, different external databases can also be utilized to analyze the bacterial 16S rRNA gene sequence for identification purposes.
At Covance, other molecular testing including PCR methods are utilized to detect resistance genes and evaluate the efficacy of the anti-infective drug. We are also implementing multiplex real-time PCR assays that provide simultaneous detection of all relevant pathogens for a clinical indication from a single specimen.
ROBUST APPROACHES TO MEET CLINICAL TRIAL NEEDS

BACTERIAL CULTURE AND ISOLATION

Microbial culture is considered a basic process in clinical microbiology but the types of specimens can vary. It’s important to select the right transport media along with optimum transport conditions to maintain the integrity of the sample and viability of the microorganism.

Achieving increased recovery of the target pathogen from specimens takes place through careful evaluation and incorporation of both the selective media and enrichment broth that are most suitable for the specimen’s target pathogen.

THE ROLE OF SUSCEPTIBILITY TESTING

Validating emerging resistance in bacterial isolates has its own challenges in clinical trials, however, multiple methods can provide accurate detection when used properly. You can choose from several antibiotic resistance measurement techniques such as broth microdilution, Kirby Bauer disk diffusion, E-test strips, and agar dilutions, plus detection of KPCs and other resistance genes. Many of these methods can be used alone or in combination to characterize bacterial resistance to antibiotics.

Covance offers both CLSI & EUCAST interpretations with strict adherence to CLSI and other regulatory guidelines to provide globally consistent data.
Quantitative cultures require counting the amount of bacteria in 1 mL or gram of a specimen. This process benefits from additional experience and expertise to obtain precise colony counts. A steady decrease of the target bacteria during consecutive visits is indicative of a successful treatment.
Specimen types can greatly vary in clinical trials. Transportation of these specimens can take days based upon the location of the site. As a result, selecting the best transport media as well as the optimum transport conditions to maintain the integrity of the sample and viability of the microorganism until it can be processed requires careful consideration.

Dedicated technical expertise is essential to evaluate and incorporate the selective media and enrichment broth that is most suitable for the specimen's target pathogen. From working with genetically engineered strains to attenuated strains or quantitative cultures, our experience can ensure a well-planned design and optimized process.

### Microbiology Clinical Trials

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THE BENEFIT OF A FLEXIBLE APPROACH, FROM END TO END

When you’re selecting a partner for your microbiology trial, it’s important to consider your laboratory’s ability to:

▶ Accommodate non-standard requests to match the protocol requirements for target pathogen isolation and identification

▶ Provide long-term storage of the pathogen for additional testing or shipment to other locations

▶ Deliver specialty reporting to document target or non-target bacteria

▶ Utilize in-house microbiology consulting experts to help you design specific processes and analyze unique specimen types

From discovery to post-marketing, you can rely on comprehensive assay services and innovative microbiology solutions from Covance and Monogram Biosciences. Together, we can help you deliver quality results and make an impact with your new antiviral drugs and vaccine candidates.

LET’S MAKE THE MOST OF INFECTIOUS DISEASE INNOVATIONS.
ABOUT THE AUTHORS

Chris Petropoulos, PhD, Chief Scientific Officer of Monogram Biosciences and Vice President, LabCorp

Chris Petropoulos is responsible for all aspects of Monogram’s antiviral drug resistance and oncology biomarker assay development activities. He is a world-recognized expert in antiviral drug resistance and molecular diagnostics and has directed the design, development and launch of 19 complex drug-resistance assays that are routinely used to inform patient treatment decisions in routine clinical settings. Dr. Petropoulos has coauthored over 160 scientific publications, is a named inventor on 14 U.S. Patents and has served as a principal investigator on 15 funding awards from the National Institutes of Health.

Pritty Patel, MS, MBA, Global Director of Microbiology, Vaccines and Novel Immunotherapeutics, Covance Laboratories

Pritty Patel provides global leadership and direction in developing Covance capabilities in clinical microbiology for anti-infective studies while also leading the continuous development of the science, strategy and breadth of departmental capabilities. She continues to develop and implement scientific and business strategy for worldwide clinical microbiology laboratories for Phase II and III clinical trials. Pritty is also responsible for implementing quality action plans.
ABOUT COVANCE

Covance, the drug development business of Laboratory Corporation of America® Holdings (LabCorp®), is the world’s most comprehensive drug development company, dedicated to advancing healthcare and delivering Solutions Made Real®. We have helped pharmaceutical and biotech companies develop each of the top 50 prescription drugs in the marketplace today.

Because of our broad experience and specialized expertise, we’re in a unique position to supply insights that go above and beyond testing. Together with our clients, we create solutions that transform potential into reality.

ABOUT MONOGRAM BIOSCIENCES

Monogram Biosciences, Inc., is a leader in developing and commercializing innovative diagnostic products to help guide and improve the treatment of human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection, and other viral illnesses, as well as cancer and other diseases. Monogram services enable health care providers to optimize treatment regimens for their patients. We also support pharmaceutical companies in developing new and improved antiviral therapeutics and vaccines and targeted cancer therapeutics.

Monogram Biosciences is a member of the LabCorp Specialty Testing Group. It was founded in South San Francisco in 1995 and became a wholly owned subsidiary of LabCorp in 2009. Monogram is a leading commercial company that performs HIV phenotypic testing. Our clinical reference lab is fully CAP- and CLIA-accredited.

Monogram provides testing for clinical patient management and drug/vaccine development, and supports clinical trials directly and as part of the Covance Drug Development team.
Learn more about our drug development solutions at www.covance.com

Covance Inc., headquartered in Princeton, NJ, USA is the drug development business of Laboratory Corporation of America Holdings (LabCorp). COVANCE is a registered trademark and the marketing name for Covance Inc. and its subsidiaries around the world.

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