FIGHTING NEGLECT

The Center for Predictive Medicine researches how to improve human health against emerging, re-emerging, neglected or rare infectious diseases by conducting basic and translational research

About one billion people – or one-sixth of the world's population – are affected by one or more neglected infectious diseases. Additionally, rare (*Burkholderia pseudomallei* and *Yersinia pestis*) and emerging pathogens (avian influenza A (H5N1)) are on the rise and constitute additional health burdens that also have serious economic impact. Because many of these illnesses initially manifest as influenza-like symptoms, effective medical intervention requires rapid diagnosis and treatment during the earliest stages of infection. This is particularly critical in containment of outbreaks, as apparent during the recent SARS and Ebola epidemics. The challenges of rapid pathogen identification and treatment call for new approaches and tools that will allow clinicians to effectively diagnose an infection to administer early lifesaving care to the patient.

The mission of the University of Louisville (UofL) Center for Predictive Medicine for Biodefense and Emerging Infectious Diseases (CPM) is to improve human health by conducting basic and translational research that leads to the development of effective diagnostic biomarkers, vaccines, antivirals and therapeutics for emerging, re-emerging, neglected or rare infectious diseases. In support of the short and long term research efforts, the CPM Regional Biocontainment Laboratory (RBL), constructed and equipped through funding from the National Institutes of Health (NIH) and the UofL, provides state-of-the-art biosafety level 3 (BSL-3) and advanced imaging technologies.

This advanced facility is managed and operated as a shared resource and provides the greater academic community with scientific expertise for the discovery of therapeutics for serious pathogens and an infrastructure to meet pandemic or bioterrorism emergency needs. The RBL, one of 11 in the US, serves as a valuable shared resource to academic, not-for-profit and private sectors for basic research and translational discovery efforts requiring BSL-2 and BSL-3 containment.

UofL RBL provides long term, affordable, sustainable, academic drug discovery efforts

Shortly after the terrorist attacks of 9/11 and the anthrax mailings in 2001, a Blue Ribbon Panel of biodefense experts convened by the National Institute of Allergy and Infectious Diseases (NIAID), a component of the NIH, described the critical need for specialised facilities to conduct research with biodefense and emerging infectious disease agents, many of which are select agents. The RBL serves as a local and national resource for drug discovery investigators from the UofL or other institutions – academics, biotechnology and industry – who can benefit from the unique mix of regulatory capability and technologies. The RBL has all the required equipment available to support microbiology, immunology and pathology efforts required for successful model and therapeutic development. Overall, this creates a unique environment to develop new tools for translationally oriented research.

The gap in the antiviral pipeline

Each year, approximately 3.9 million people die from respiratory infectious diseases caused by viruses. Remarkably, there are few treatments available for the majority of human viruses, vaccine or antiviral. An exhaustive search for drugs that have antiviral therapeutic indication, and were approved in the United States (FDA) and European Union (EMEA), retrieves 48 drugs containing 42 unique, active pharmaceutical ingredients. The number of licensed antiviral drugs has grown to over 62 in the past few decades, and the corresponding annual market for antivirals has grown to $18bn per year. However, the majority of these drugs are for treatment against HIV-1 (AIDS), followed by hepatitis B and C and influenza viruses. Most drugs on the market target viruses that cause persistent infections (HIV, HBV, HCV and herpes viruses). Unfortunately, the drug pipeline for acute viral infections does not receive substantial attention from the biopharmaceutical sector. Hence a critical gap exists in the availability of small molecules for treatment of the majority of viral infections.

Researchers at the UofL have taken advantage of government programmes to address this gap. Most recently, the NIH Molecular Libraries Program (http://mli.nih.gov/mli/mlpcn/mlpcn/) fostered the creation of large and specialised academic centres (i.e. Molecular Libraries Probe Production Centers Network, MLPCN) to provide current,

state-of-the-art high throughput screening (HTS) and medicinal chemistry approaches and support in molecular probe discovery for various disease targets. A decade ago, HTS approaches in drug discovery were typically only available in the pharmaceutical industry.

Building upon the small molecule probes identified and patented through the MLPCN programme, researchers from the UofL CPM, Drs William Severson, Colleen Jonsson and Donghoon Chung, and the University of Kansas, Dr Jennifer Golden, are working collaboratively to advance newly discovered lead compounds for diseases caused by Venezuelan equine encephalitis virus (VEEV) and respiratory syncytial viruses (RSV).

The New World alphaviruses, VEEV and eastern and western equine encephalitis viruses, are RNA viruses that are endemic throughout the Americas. They cause encephalitis in humans and equines, thus presenting serious health and economic threats as emerging pathogens. Despite the urgent need, neither approved drugs nor vaccines are available for treatment of these diseases in humans.

RSV is an increasingly important paediatric pathogen as the most common cause of bronchiolitis and pneumonia among infants and children under one year of age. Globally, there are approximately 3 million hospitalisations of children under five years of age and 200,000 deaths due to RSV or its complications each year. Even so, RSV disease may occur at any age, and severe disease can affect those individuals who have chronic obstructive pulmonary disease (COPD) and the immunocompromised. There is no vaccine commercially available and supportive care is the main therapy. Therapeutic options are few.

Leveraging molecular imaging to advance animal models for rare and emerging infectious diseases

Imaging methods that visualise the structure and function of the living body are widely used in clinical and biomedical research settings. The full potential of these methods has not been fully realised in regards to the study and treatment of the diseases caused by infectious agents. PET/SPECT (positron emission tomography/single photon emission computed tomography) imaging modalities provide a new opportunity to study in real time the pathophysiology of pathogen infection, resulting from pathogen replication and dissemination, and the host response to infection.

A cornerstone of the RBL is the state-of-the-art imaging facilities available for real-time, whole body animal imaging. Major imaging modalities include two state-of-the-art instruments: a Siemens tri-modality scanner and a Caliper Life IVIS Spectrum. The five imaging modalities are microPET, microSPECT, microCT (computed tomography), bioluminescence and fluorescence. The UofL RBL has an imaging suite at ABSL-3 with instrumentation capable of real-time, whole body animal imaging, either in 2D or 3D, using both radionuclide and optical imaging approaches.

New approaches and research being developed at the UofL seek to advance not only our understanding of drug distribution and real-time pathophysiology of pathogen infection, but also the acceleration of efficacy studies in small animal models of infectious disease. Modern imaging technologies available at the UofL ABSL-3 open a new door in the study of rare and emerging

infectious disease in animal models. Importantly, the animal models that are developed can be employed to accelerate the discovery of targets and drugs for therapeutic intervention, and biomarkers that could be used for early diagnosis.

Animal models developed in these proof-of-concept studies will provide a framework to promote models for other neglected and emerging infectious diseases requiring high containment. Ultimately, these efforts can reveal early and differential markers predictive of a broad array of bacterial and viral infections, creating a new platform for discovery of novel diagnostics and therapeutics. Broadly, the methods, probes and models developed in the studies proposed here provide the critical underpinnings that scientists and clinicians can use to advance the discovery of new diagnostics and therapeutics, monitor disease progression and evaluate treatment response.

Current multi-collaborative efforts by the UofL CPM include Dr Jonsson's focus on development of mouse and ferret models of H1N1 pandemic influenza infection using CT/PET to understand the temporal dynamics of influenza-driven inflammation. Drs Jonathan Warawa and Matthew Lawrenz are currently using optical imaging methods in the study of *B. pseudomallei* and *Y. pestis* pathogenesis. Dr Haixun Guo, a radiochemist, is currently pursuing the development of novel radionuclide probes. Probes will be evaluated in their ability to reveal the host response to infection both temporally and spatially in real time. The extraordinary sensitivity of these new probes holds promise to pinpoint the earliest moments of host response and critical paths of disease progression.

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