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Scientific Session Speaker Abstracts

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Area of Focus

Innovations in Clinical Microbiology

A Translational Approach to Antimicrobial Resistance

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Antimicrobial resistance (AMR) in bacterial and fungal pathogens is a top public health priority highlighted by the World Health Organization and other prominent public health entities. In 2019, AMR pathogens caused an estimated 2.8 million infections and >35,000 deaths in the U.S., and 4.95 million associated- and 1.27 million attributable-deaths worldwide. Among AMR pathogens, ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.) cause the majority of nosocomial infections and are associated with the highest risk of mortality and long-term disability due to their AMR profiles. The AMR situation is complicated by inherent complexities of the health ecosystem in each country and access to antimicrobial therapies. Moreover, AMR is a "normal" evolutive step in any given microorganism; therefore, resistance is the norm rather than the exception.

Understanding the molecular epidemiology and mechanistic basis of resistance opens new possibilities for diagnosis and treatment of the most recalcitrant infections. Indeed, AMR often emerges in hospitalized patients who are critically ill or immunosuppressed and are often subjected to heavy antimicrobial use as life-saving interventions. Our latest work has focused on several organisms including, 1) multidrug-resistant enterococci, 2) carbapenem and cephalosporin-resistant Enterobacterales and 3) *Staphylococcus aureus*. Our mechanistic work in enterococci and *S. aureus* has yielded a deeper understanding of the cell envelope response to antibiotics and antimicrobial peptides, providing new insights with the potential to deploy new diagnostic and therapeutic tools. Using genomics, we have discovered novel mechanisms of dissemination of AMR organisms in both the developed and developing countries and detected phenotypes that were not previously identified. This translational approach centered on a mechanistic framework has permitted actionable interventions that can potentially be scaled up to tackle the AMR crisis around the world.

Liver-Based Vaccine Protection Against Invasive Bacterial Diseases

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Invasive pneumococcal disease (IPD) represents a significant cause of human morbidity and mortality. Two types of capsular polysaccharide vaccines have been licensed in many countries for the prevention of IPD: pneumococcal polysaccharide vaccine (PPV) and pneumococcal polysaccharide conjugate vaccine (PCV).A large body of literature has documented the protectiveness of these vaccines, but it remains largely unknown how these vaccines enhance the host's capacity to clear invasive bacteria once they enter the blood circulation. The current paradigm is that circulating phagocytes are responsible for eliminating invasive pathogens that are opsonized by vaccine-elicited antibodies. We have recently discovered that PPV- and PCV-elicited immunity against invasive pneumococci mainly operates in the liver in a vaccine type-specific manner. In a mouse sepsis model, PCV confers far superior protection compared to PPV. PCV induces a high level of IgG antibodies, and thereby enables the liver resident macrophage Kupffer cells (KCs) and sinusoidal endothelial cells (ECs) to capture and eliminate the otherwise "uncatchable" blood-borne pneumococci in the liver sinusoids. In contrast, PPV immunization elicits a relatively lower level of IgM antibodies, which activate bacterial capture of only KCs (but not EC's). These liver-based vaccine protection mechanisms have also been confirmed with the polysaccharide conjugate vaccine for *Neisseria meningitidis* and investigational vaccines. Our findings not only provide a comprehensive explanation for vaccine/antibody-boosted immunity against invasive bacteria but may also serve as in vivo functional readouts of vaccine efficacy.

Plasmids as Cross-Ecological Sources of Antimicrobial Resistance in Humans, Animals and the Environment

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The ability to trace the circulation of resistance determinants located on plasmids within different bacterial populations helps clarify the routes by which antimicrobial resistant bacteria and their related genes can spread. Plasmids evolved acquiring multiple, critical resistance genes. Conventional plasmid typing has been widely used in the last decade, but genomics is now identifying and characterizing an impressive number of plasmids.

These data brought novel knowledge on horizontal transfer of clinically relevant antimicrobial resistance genes among different bacterial lineages. Epidemiological information contributed to the identification of "epidemic" plasmids that spread worldwide in different bacterial species. The extensive use of whole genome sequencing (WGS) has helped to identify and describe the dynamics of plasmid-mediated transmission of antimicrobial resistance genes within hospital environments and between food-producing animals and humans. WGS has also helped to trace the evolution of plasmids circulating in different sources and reservoirs. Phylogenetic analysis of bacterial genomes, combined with plasmid typing and epidemiological data can clarify the circulation and spread of specific clinically relevant genetic determinants, such as those conferring resistance to newest generation cephalosporins, carbapenems and new antibiotic/inhibitor combinations.

Unveiling the Dark Side of Oral Treponema

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The oral bacterium *Treponema denticola* is a keystone pathogen not only associated with periodontitis, but also with several human systemic diseases such as oral cancer. However, *T. denticola* is understudied. Thus far, only a handful of bacterial virulence factors have been functionally characterized in *T. denticola*. We recently solved the secretome of *T. denticola* and identified several new virulence factors including a dual domain protein with a N-terminal bacterial Ig-like (Big) domain and a C-terminal Mac-1 domain. We found that the C-terminal Mac-1 domain functions as a cysteine protease and disarms the complement system through degrading several key complement factors such as C3. The N-terminal Big-like domain inhibits neutrophils chemotaxis and activation and renders bacteria protection against neutrophils phagocytosis. Collectively, this protein supports bacteria immune evasion against both complement killing and neutrophil phagocytosis.

Epidemiology and Prevention Strategies for Carbapenem-Resistant Enterobacterales

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Antimicrobial resistance (AMR), a pressing global health threat, has emerged in recent decades, jeopardizing the efficacy of antibiotics and posing a significant challenge to clinical medicine. Among the most formidable AMR threats, carbapenem-resistant Enterobacterales (CRE) have garnered particular attention due to their high mortality rates, prolonged hospital stays and increased health care costs. The rates of carbapenem resistance in Enterobacterales have escalated from 2.1% in 2005 to 11.1% in 2023. Notably, the patient-based disease burden in tertiary hospitals in China is severe, with an overall incidence of 4.0 per 10,000 discharges across 25 tertiary hospitals. The ST11-KL64 carbapenem-resistant *Klebsiella pneumoniae* (CRKP) clones have demonstrated remarkable expansion, rising from 1.54-46.08% between 2011 and 2021. Global phylogenetic analysis has revealed that ST11-KL64 CRKP has evolved into a virulent and highly resistant clade, exhibiting notable regional dissemination. Single-nucleotide polymorphism (SNP) analysis has identified BMPPS (including *bmr3*, *mltC*, *pyrB*, *ppsC* and *sdaC*) as a key marker for this clade. The BMPPS SNP clade is associated with high mortality rates and possesses robust anti-phagocytic and competitive properties in vitro. To address the CRE epidemic, a multifaceted approach is necessary, encompassing robust infection prevention and control measures, judicious use of antibiotics, enhanced surveillance systems and the development of novel therapeutic strategies. Research into new antibiotics, alternative treatments such as phage therapy and strategies to combat AMR at the molecular level holds promise for mitigating the impact of CRE and preserving the effectiveness of antimicrobials in the face of this formidable challenge.

Area of Focus

Bacterial and Viral Pathogenesis

Pathogenesis of Campylobacter-Induced Systemic Infection

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Campylobacter jejuni is a major enteric pathogen and is responsible for a large number of foodborne illnesses worldwide. As an enteric organism, *C. jejuni* normally colonizes the intestinal tract and induces localized inflammation and disease. However, some hypervirulent strains of *C. jejuni* are able to translocate across the intestinal epithelium and cause systemic infection or even clinical abortion in pregnant hosts. Recently, our group identified a hypervirulent and antibiotic-resistant clone of *C. jejuni* that is emerging in the U.S. We showed that this clone has a unique ability to induce systemic disease compared to other *C. jejuni* strains. Although production of capsule is necessary for hypervirulence, it is primarily related to survival in blood and is not sufficient for inducing clinical abortion. Using genome-based population genetics and bottleneck selection provided by an animal model, we discovered that specific amino acid substitutions in the major outer membrane protein (MOMP) are critical for the hypervirulent phenotype. The mutations in MOMP likely contribute to the intestinal translocation step or the tropism of *Campylobacter* toward placental tissues. Once reaching the utero-placental unit, *C. jejuni* multiplies rapidly, triggers a massive proinflammatory response from the host and inhibits fetal development, resulting in premature birth or abortion. These findings provide critical insights into the pathogenesis of *Campylobacter*-induced systemic infections and identify potential targets for the development of anti-*Campylobacter* vaccines.

Influenza in High-Risk Populations: Impact on the Virus

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Persons with obesity and other metabolic syndromes are at higher risk for developing severe complications upon influenza infection. My group and others have begun to decipher the mechanism(s) for the increased disease severity, demonstrated that vaccine responses are less effective in obese hosts, identified the impact of weight loss on vaccine responses and investigated the use of antivirals in this target population. Yet, little work has been done to explore the impact that this unique microenvironment may have on the virus. In is presentation, we will share data demonstrating how obesity impacts intra- and inter-host viral evolution, including changes in single nucleotide variants, generation of defective viral genomes and overall viral diversity, and how this impacts influenza virus drift and shift.

Vibrio cholerae and Aladdin's Magic Carpet

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The individual-specific commensal microbial community of the gut, the gut microbiota, plays an important role in mediating resistance against pathogen colonization. In areas endemic for the important human diarrheal disease cholera, the microbiota is subject to numerous and recurrent environmental insults that lead to regular community damage, or dysbiosis, characterized by high levels of *Streptococcus* species. This dysbiotic community is known to be less able to resist colonization and repress virulence gene activation by *Vibrio cholerae*, the etiologic agent of cholera, but how dysbiosis can drive increased virulence in enteric pathogens is much less well understood.

In this study, we show that not only is the dysbiotic gut microbiota susceptible to *V. cholerae* infection, but also that human primary isolate and type strain streptococci are able to promote elevated *V. cholerae* virulence, gut colonization and epithelial attachment by the production and secretion of short hydrophobic peptides that we name SVIP for their effect on *V. cholerae* pathogenesis. While SVIPs are previously known as streptococcal species-specific diffusible signals for quorum sensing gene regulation, here we describe a novel post-translational mechanism whereby SVIPs induce cellular hypermotility independent of transcriptional regulation, not only in *V. cholerae,* but also diverse other bacterial taxa. We identify the specific molecular interaction between SVIP and the flagellar stator that responds to sodium electrochemical gradients in *V. cholerae* responsible for this effect and show that SVIP production by streptococci can modulate the overall community assembly of complete human microbiota in germfree mouse colonization. These findings show that signaling peptides previously thought to be highly specific in microbial targets are, in fact, able to manipulate the behavior of divergent prokaryotic lineages, highlighting the complexity of microbial host-associated community interactions and their implications for personalized disease outcomes.

Host Factors Affect Transmission and Pathogenesis of Avian Influenza Viruses

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Avian influenza viruses (IAVs) periodically cross the species barrier and infect humans. While such spillover events are rare, they may represent a source of new pandemic virus strains. The zoonotic influenza H7N9 virus has acquired several features necessary for adaptation to mammalian hosts, including altered HA receptor specificity and enhanced viral polymerase activity. Still, the molecular mechanisms enabling cross-species transmission of avian IAVs remain incompletely understood.

We used whole-genome sequencing to compare H7N9 patients with healthy controls and observed a strong association between H7N9 infection and rare, heterozygous single nucleotide variants (SNVs) in the *MX1* gene. *MX1* codes for myxovirus resistance protein A (MxA), an interferon (IFN)-induced antiviral GTPase known to control IAV infections in transgenic mice. The majority of the MxA variants identified lost the ability to inhibit avian IAVs, including H7N9, in transfected human cell lines. Most of the inactive MxA variants exerted a dominant-negative effect on the antiviral function of wild type (wt) MxA, suggesting an MxA null phenotype in heterozygous carriers. Our study provides genetic evidence for a crucial role of the *MX1*-based antiviral defense in controlling zoonotic IAV infections in humans.

A Naturally Isolated Symbiotic Bacterium Suppresses Flavivirus Transmission by Aedes Mosquitoes

Gong Cheng, Ph.D.
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The commensal microbiota of the mosquito gut plays a complex role in determining the vector competence for arboviruses. Here, we identified a bacterium from the gut of field *Aedes albopictus* mosquitoes, named *Rosenbergiella* sp. YN46 (*Rosenbergiella*_YN46), that rendered mosquitoes refractory to infection with dengue and Zika viruses. Inoculation of *Rosenbergiella*_YN46 into *A. albopictus* mosquitoes effectively prevents viral infection. Mechanistically, this bacterium secretes glucose dehydrogenase (*Ry*GDH), which acidifies the gut lumen of fed mosquitoes, causing irreversible conformational changes in the flavivirus envelope protein that prevent viral entry into cells. In semi-field conditions, *Rosenbergiella*_YN46 exhibits effective transstadial transmission in field mosquitoes, which blocks transmission of dengue virus by newly emerged adult mosquitoes. The prevalence of *Rosenbergiella*_YN46 is greater in mosquitoes from low-dengue areas than in those from dengue-endemic regions. *Rosenbergiella*_YN46 may offer an effective and safe lead for flavivirus biocontrol.

Evolution and Entry Mechniasm of SARS-Related Coronaviruses From Wildlife

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In the past 20 years, 2 different strains of SARS-related coronaviruses (SARSr-CoV), SARS-CoV and SARS-CoV-2, have caused pandemics. Both of them are considered to have a bat origin, as the closely related CoVs were discovered in bats. Furthermore, civets and pangolins were considered as accident hosts of SARS-CoV- and SARS-CoV-2-related viruses. Bat SARSr-CoV are carried by different *Rhinolophus* species, which are only distributed in the Old World.

Our group collected around 1,000 SARSr-CoVs positive samples from bats in the past 20 years and found phylogenetically close relatives of SARS-CoV and SARS-CoV-2 in restrict areas of Yunnan province. Phylogenetic analysis of known SARSr-CoV sequences found by us and other teams indicates that bat SARSr-CoVs are divided into at least 7 sublineages with different geographic distributions.

Bat SARSr-CoVs show similar evolution pattern as SARS-CoV-2, but higher genetic diversity. The major differences of these SARSr-CoV are in the spike proteins, which are responsible for virus entry, induce the neutralization antibody and pathogenicity. SARS-CoV-1 and -2 utilize the same receptor ACE2, while bat SARSr-CoVs can be divided into ACE2-dependent and-independent group. Some ACE2-dependent bat SARSr-CoVs have a high binding affinity to human ACE2 and efficiently infect human ACE2 transgenic mice and wild type hamsters showing different severity of lung damage. These results showed that some bat SARSr-CoVs have potential interspecies transmission. Active surveillance and countermeasures should be prepared in advance.

Precision Design of Vaccines for Broad Protection

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Westlake University

Our team has developed a high-throughput functional analysis method for viral mutants, with enhanced sensitivity and specificity, providing inspiration and novel perspectives to virology research. The method offers precise detection/scanning across the whole viral genome, which makes site-specific modifications possible and allows more comprehensive investigation of topics, including drug resistance, immune escape and more. It has been applied to design a new attenuated influenza vaccine, which induces efficient immune responses and is proved to be safe in an animal model. More importantly, the T cell response aroused in response to the vaccine targets the conserved regions of influenza virus, allowing for recognition of diverse strains of influenza virus.

This platform provides potential for not only the elimination of viral infection, but also immunosuppressive solid tumors. Vaccines targeting tumor antigens can be designed to induce immunity against tumors, shedding light on cancer mechanism investigation and cancer vaccine development. In addition, our team has established a high-throughput antibody-epitope detecting platform for evaluating the protective effects of infection and vaccination, as well as other disease settings.

Area of Focus

Pathogen-Host Dynamics

Barrier-Cell Inflammasome Activation and Pyroptosis in Antibacterial Defense and Sepsis

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The canonical (caspase-1) and noncanonical (caspase-4/5/11) inflammasomes both cleave gasdermin D (GSDMD) to induce pyroptosis. Whereas caspase-1 processes IL-1β and IL-18 for maturation, no cytokine target has been firmly established for LPS-activated caspase-4/5/11. Here, we show that activated human caspase-4, but not mouse caspase-11, directly and efficiently processes IL-18 in vitro and during bacterial infections, which mainly occurs in epithelial cells.

Crystal structure of the caspase-4/pro-IL-18 complex reveals a binary substrate-recognition mechanism, including a unique exosite that binds to a specific structure formed jointly by the propeptide and post-cleavage-site sequences in pro-IL-18. In caspase-11, a structural deviation around the exosite underlies its inability to target pro-IL-18, which can be restored by rationally designed mutations. The structure of pro-IL-18 features autoinhibitory interactions between the propeptide and the post-cleavage-site region, preventing recognition by the IL-18Rα receptor. Meanwhile, we also find that GSDMD activation by LPS-ligated caspase-4/11 specifically in brain endothelial cells, but not TLR4-induced cytokines, mediates BBB (blood brain barrier) breakdown in response to circulating LPS or during LPS-induced sepsis.

Electron microscopy records ultrastructural changes in the disrupted BBB, including pyroptotic endothelia, abnormal appearance of tight junctions and vasculature detachment from basement membrane. Delivery of active GSDMD into brain endothelial cells bypasses LPS stimulation and opens the BBB. In *CASP4*-humanized mice, Gram-negative *Klebsiella pneumoniae* infection disrupts the BBB, which is blocked by a GSDMD-neutralizing nanobody expressed in brain endothelial cells. These findings together shift the paradigm in the understanding of noncanonical-inflammasome-mediated antibacterial defenses and sepsis.

Host Pathways Controlling Human Cytomegalovirus Latency and Reactivation

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Human cytomegalovirus (CMV) is a herpesvirus infecting the majority of the population worldwide. CMV establishes a life-long infection in individuals by way of viral latent infection that is marked by sporadic and typically subclinical reactivation events. While the virus typically persists asymptomatically in immune competent adults, it is a significant cause of life-threatening disease in the immune compromised (e.g, stem cell and solid organ transplant recipients) and can cause life-long disability in the context of congenital infection. Defining the mechanisms that control entry into and exit from latency is key to controlling CMV disease. Our research program is focused on defining virus-host interactions that define programs of viral latency and reactivation.

Host factors important for CMV latency and reactivation programs are typically regulated by differentiation, suggesting that CMV has evolved to sense and respond to changes in the cell associated with differentiation. For example, we have shown that the virus controls the trafficking and signaling of the major homeostatic regulator, epidermal growth factor receptor (EGFR). Host transcription factors downstream of EGFR drive the expression of viral genes important for latency. CMV drives EGFR degradation to attenuate signaling for reactivation. Similarly, a viral protein critical for reactivation, UL136p33, is susceptible to the host E3 ligase, inducible degrader of low-density lipoprotein receptor (IDOL). IDOL is induced by liver X receptor signaling, which is responsive to cholesterol, and is highly expressed in hematopoietic progenitor cells (HPCs) where the virus establishes latency. The IDOL-induced instability of UL136p33 is critical for the establishment of latency. Upon differentiation, IDOL levels decrease and loss of IDOL-mediated degradation of UL136p33 is important for reactivation.

Through these and other studies, a complex picture of latency and reactivation emerges whereby host factors control the expression and accumulation of viral gene products in a differentiation-specific manner, which allows the virus to sense and respond to changes in the host cell for maintaining latency or re-entering the replicative cycle. These studies identify both viral proteins and host pathways, including EGFR and LXR signaling, important to controlling CMV latency and reactivation.

The Regulation of the KSHV Life Cycle

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Kaposi's sarcoma-associated herpesvirus (KSHV) is a large double-stranded DNA virus, with a 165kb genome encoding about 90 open reading frames. After the primary infection, KSHV can establish lifelong latent infection in the host, and there is no effective drug to clear it from the body. KSHV mainly infects endothelial cells and B lymphocytes in host and can induce Kaposi's sarcoma (endothelial origin), primary effusion lymphoma (B cell origin) and multicentric Castman's diseases (B cell origin) under certain conditions through long-term interaction with the host. The establishment of lifelong latent infection of KSHV in the host is a necessary condition for its tumorigenesis, but the molecular mechanism of latent infection regulation and tumorigenesis of KSHV has not been fully elucidated. This report will mainly discuss the mechanism of KSHV life cycle regulation based on our research progress.

Modulation of Innate Immunity by Dengue Viruses and Vaccines

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Dengue virus (DENV) belongs to the *Flaviviridae* family and is endemic in more than 120 countries in the world. There are 4 different serotypes, named DENV1, DENV2, DENV3 and DENV4, that co-circulate and can cause annual epidemics in tropical and subtropical areas of the world and are transmitted to humans by *Aedes* spp. mosquitoes. We and others have shown that DENV can efficiently inhibit the generation of innate immune responses in infected cells by blocking both the production and signaling of type I interferons (IFN) in susceptible cells, including dendritic cells (DCs).

We found that the DENV protease complex (NS2B3) cleaves different innate immune factors in infected cells, such as STING and cGAS, which results in the inhibition of type I IFN production and of antiviral responses. Live attenuated versions of the 4 serotypes of DENV were generated by the NIH/NIAID and, when tested in a tetravalent formulation (LATV) in clinical trials, showed strong immunogenicity, remarkable seroconversion for all 4 serotypes in vaccinated individuals and a satisfactory safety profile.

We used DENV and attenuated DENV (vaccine viruses) to infect primary human DCs. Samples were analyzed by spectral multi-parameter flow cytometry for activation markers, multiplex ELISA for cytokine/chemokines and RNaseq for transcriptomics analyses. The 4 DENV serotypes can induce different immune responses in primary DCs after infection ex vivo. In particular, DENV-4 shows a strong induction of innate immune cytokines and activation markers in DCs, as compared with DENV-2. These serotype specific innate immune profiles were also observed when using individual dengue viruses present in the NIH-LATV formulation. Our data strongly suggest that the non-structural proteins of DENV-4 may be responsible for the strong innate immune profile induced by the dengue LATV tetravalent vaccine formulation in human DCs.

Environmental Adaptation of Environmental Human Fungal Pathogens

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The vast majority of fungi that can infect humans are environmental human fungal pathogens. How the environmental adaptability of these fungi affects their reproduction, infection and survival during antifungal treatment is a pivotal question in terms of fungal pathogen biology. This is the focus of our research. We revealed the central signaling pathways of different reproductive strategies of clinically important environmental human fungal pathogens, providing the first evidence for quorum sensing-driven sexual (meiotic) reproduction (*Nat Microbiol*, 2018; *eLife,* 2018*; Annu, Rev Microbiol*, 2021; *PLoS Genet*, 2021; *Nat Commun*, 2022; *The Innovation*, 2024). We identified a new human fungal pathogen capable of producing hypervirulent variants through host temperature-driven mutagenesis (*Nat Microbiol*, 2024a). We showed that brain glucose induces fungal tolerance to amphotericin B during fungal meningitis, revealing the novel form of antifungal tolerance (*Nat Microbiol*, 2024b). We also demonstrated that highly fungicide-tolerant fungal persister cells can form during fungal lung infections and identified the first FDA drug with potent activity against fungal persister cells (*Adv Drug Deliv Rev*, 2023; *Cell Host & Microbe*, 2024). Our group is now studying the mechanisms of virulence and antifungal tolerance driven by environmental or host factors.

Kill Fungi: The Type VI Secretion System and its Effectors Offer a Microbial Solution to Combat Drug-Resistant Fungal Pathogens

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Bacterial-fungal interactions are critical determinants of microbial community dynamics and host health. The alarming rise in fungal infections, particularly those resistant to existing antifungal treatments, underscores the urgent need for innovative treatment strategies. The type VI secretion system (T6SS) is a spear-like contractile weapon employed by many gram-negative bacteria for interspecies interactions, including a few anti-fungal T6SSs. The T6SS functions by injecting toxic effectors into neighboring species, capable of penetrating the cell envelopes and achieving cytosol-to-cytosol delivery. Here, I will introduce common strategies the T6SSs use to kill competitors and novel effector functions, specifically for anti-fungal activities. These recent findings may offer new insights into bacterial-fungal interactions and potential strategies to combat fungal drug resistance.

Herpesviruses: Tool Viruses, Visible Infection Models and Large Capacity Vectors

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Establishing latency after primary infection and latency-reactivation are the features of herpesviruses. Studying these features is complicated, especially for neurotropic herpesviruses since their site of latency is neural ganglions. To better understand herpesvirus infection status and progress, pathogenesis, disease features and treatment, we modify the viruses to create tool viruses. These viruses allow us to visualize infection and trace/monitor infection status and progress. The tool viruses include herpes simplex virus 1 and 2 (HSV-1, HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV) and murine cytomegalovirus (MCMV). HSV and CMV can be large capacity viral vectors for gene therapy, vectored-vaccine and oncolytic virotherapy. Moreover, given herpesvirus coinfection in certain individuals—such as people with COVID-19, cancer patients and transplantation recipients—causes lethal outcomes, our tool viruses and visual infection models are critical for advancing herpesvirus investigations to promote human health.

Area of Focus

Vaccines and Therapeutics

Development of Broad-Spectrum Antiviral Drugs to RNA Viruses of Pandemic Risk

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Emerging viruses pose a significant threat to human health as exemplified by the 3 novel coronaviruses that emerged in the last 20 years, including the severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2, the virus driving the ongoing coronavirus disease 2019 (COVID-19) pandemic. Although the emergence of new viruses and outbreaks of previously unknown diseases are destined to happen in the future, specific viral pathogens cannot be predicted. Therefore, development of broadly effective antiviral drugs is highly needed to prevent and combat future emerging viral diseases.

In this report, we will introduce the virus types with potential pandemic-risk and strategies for development of broad-spectrum antiviral drugs. We will use SARS-CoV-2 as an example for antiviral drug study. We designed and developed the RdRp-targeting 5'-hydroxyl-isobutyryl prodrugs, ATV006 and ATV014 (SHEN26), which showed excellent oral bioavailability in rats and cynomolgus monkeys and exhibited potent antiviral efficacy against different SARS-CoV-2 variants of concern (VOCs) and other coronaviruses. We also developed a first-in-class anti-SARS-CoV-2 drug candidate MI-54, which targets the 2'-O-methyltransferase of coronaviruses.

Current Status and Trends of Therapeutic Vaccines for the Treatment of Chronic Infectious Diseases by Persistent Infectious Pathogens

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Vaccination is an effective and easy method for combatting infectious diseases. Widespread use of prophylactic vaccines has led to the eradication of smallpox and elimination or control of diseases like polio, measles, mumps, tetanus, diphtheria and whooping cough in most regions of the world.

Nowadays, chronic infectious diseases, including viral diseases caused by human immunodeficiency virus (HIV), hepatitis B virus (HBV) and Epstein-Barr virus (EBV), and bacterial disease, like tuberculosis, are the main cause of morbidity and mortality globally. Chronic infections are difficult to cure with monotherapy, and long-term treatment may lead to the emergence of drug-resistant strains. Therapeutic vaccines offer a potentially effective strategy that utilizes the body's immune system to alleviate infection symptoms or prevent the reactivation of pathogens. Yet development of therapeutic vaccines is less abundant than preventive vaccines, and the evidence is limited.

Development of therapeutic vaccines requires the establishment of clear concepts and standardized methods for evaluating vaccine efficacy for each chronic infectious disease. Recently, human papillomavirus (HPV) preventive vaccines are available, but have limited effectiveness for already HPV-infected patients. EBV infection is associated with various cancers and chronic EBV infections. Therapeutic vaccines primarily target the latent proteins expressed during EBV latency and help to strengthen the efficacy of current treatments. Cytomegalovirus (CMV) infection can persist for a long time, and therapeutic vaccines primarily target the capsid proteins that can neutralize virus particles of CMV. Varicella-zoster virus (VZV) can cause chickenpox and shingles. Therapeutic vaccines require high doses of antigens to suppress virus recurrence. HBV and HIV are the most difficult to eradicate viruses because of the reservoir of virus within target cells, and the goal of therapeutic vaccines for chronic HBV infection is to achieve "functional cure." Recently, some “sandwich” or new cocktail therapy with therapeutic vaccines to achieve functional cure have shown some promising efficacy in the clinical trials.

Sequential SARS-CoV-1 and SARS-CoV-2 Infections Expand Antibody Response to Conserved Sites on the Spike Glycoprotein

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The first severe acute respiratory syndrome coronavirus (SARS-CoV-1), identified in 2003, causes more severe disease than its close relative SARS-CoV-2, which is responsible for the recent COVID-19 pandemic. Both viruses utilize the same host cell receptor, angiotensin-converting enzyme 2 (ACE2), via their spike protein receptor-binding domain (RBD). However, our understanding of the human antibody response to these 2 pathogenic coronaviruses remains incomplete. Leveraging a unique cohort of patients who were infected with SARS-CoV-1 in 2003 and subsequently with SARS-CoV-2 in 2023, we conducted a systematic analysis of the antibody response from both polyclonal and monoclonal perspectives.

Our results demonstrate that prior SARS-CoV-1 infection significantly broadens the antibody response to a diverse array of coronavirus variants following SARS-CoV-2 infection. Notably, there was a significant increase in monoclonal antibodies (mAbs) targeting the more conserved Class 4 and Class 5 antigenic sites on the RBD, as opposed to the highly variable Class 1 and Class 2 sites predominantly targeted in individuals primarily infected with SARS-CoV-2.

These findings illustrate that pre-existing antibodies to SARS-CoV-1 can modulate the antibody response to subsequent SARS-CoV-2 infection. Molecular characterization of antibody breadth, specificity and ontogeny will enhance our understanding of complex antibody responses in humans and inform the design of more effective intervention strategies against a broad range of human and animal coronaviruses.

Characterize Adaptive Immune Responses and New Curable Strategy During Virus Infection

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Viruses, such as SARS-CoV-2 and hepatitis B virus (HBV), which cause acute and chronic infection, respectively, have seriously endangered human health, and a lack of effective therapeutic strategy remains. Although vaccines and neutralizing antibodies have been authorized for emergency use of SARS-CoV-2, the recent increasing prevalence of mutant variants has caused serious threats and challenges.

We used single-cell omics technology to comprehensively characterize neutralization antibody and SARS-CoV-2-specific T cell responses for the development of future vaccines against COVID-19.

In addition, although effective treatments are available for chronic hepatitis B (CHB), functional cure is hardly achieved. We dissected the unknown immune factors responsible for a functional cure in a unique cohort of pediatric CHB patients, exposed toIFNα treatment, which had a higher rate of functional cure.

In response to IFN-α treatment, the most significant alterations occurred in antibody-secreting cells. Particularly, the early generation of HBV-specific IgG3 were robustly associated with the functional cure in our cohort of pediatric CHB patients. These findings significantly expanded our understanding on the immunological factors regarding the B cell responses during the critical period of HBsAg seroconversion, which may greatly facilitate the development of more effective treatments.

Protein Vaccine Against Pneumococcus Infection

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Protein based pneumococcal vaccine (PBPV) is recognized for its potential to offer cross-serotype protection. CanSinoBio 's vaccine candidate, based on the PSPA+PlyLD antigens, has shown promising safety and immunogenicity in early-stage clinical trials. Phase Ia trial in adults and Phase Ib trial in the elderly demonstrated a strong immune response, as indicated by IgG antibody levels following a single dose, even in the presence of relatively high baseline antibodies. Functional antibody analysis using the MOPA assay revealed generally higher antibody levels compared to PPV23, though the response varied across different target bacterial strains. While these findings are encouraging, they also highlight the limitations of MOPA—a classical method for detecting polysaccharide-specific antibodies—in assessing functional antibodies generated by protein-based vaccines. These results have prompted us to explore new hypotheses and approaches in our future research.