



Impact of Infectious Disease on Humans & Our Origins

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ABSTRACTS

SARS CoV2: A Third Coronavirus Takes to the Air **Robert (Chip) Schooley, UC San Diego**

Over the past two decades, novel coronaviruses have spilled from the bat to the human population on three occasions. The first two breakouts in south China in 2003 and in Saudi Arabia in 2012 launched the SARS and MERS outbreaks, respectively. Both outbreaks were contained by aggressive case finding, contact tracing and quarantine activities. A third crossover of a novel coronavirus into the human population occurred in the fall of 2019. This event which is believed to have occurred around a wet market in Wuhan, China was, unfortunately, not efficiently contained and spread rapidly across China. Since its crossover events six months ago, the virus has infected over 4 million people and resulted in 300,000 deaths. Although progress is being made on both the drug and vaccine fronts, the main tool with which the human population has been seeking to contain the virus, social isolation, has been only partially effective and has resulted in major economic damage to the global economy. This presentation will focus on the biology, pathogenesis and epidemiology of the SARS-2 coronavirus and containment efforts to date.

Dengue and Zika: Mosquito-borne viral infections **Sujan Shresta, La Jolla Institute for Immunology**

The four dengue virus serotypes and Zika are closely related RNA viruses that share the same mosquito vector and circulate in overlapping geographic ranges. Due to urbanization and climate change, dengue- and Zika-transmitting mosquitos are expanding their habitat, and these viruses now pose significant threats to global health, affecting over half the world's population. Due to their phylogenetic and antigenic relatedness, the immune response to dengue and Zika viruses are highly cross-reactive. These cross-reactive immune responses may play a protective or pathogenic role depending on the context, such as the sequence of viral infections or interval between viral infections. Thus, the dengue/Zika field has been focused on addressing the following questions related to the immunological cross-reactivity between the dengue serotypes and Zika: 1) why has it been challenging to develop a dengue vaccine despite 70 years of effort? 2) how does a previous exposure to dengue virus influence subsequent infection with Zika virus? 3) How does a prior exposure to dengue virus impact Zika viral evolution? Our studies using dengue mouse models have demonstrated that antibodies can increase dengue infection and convert a mild illness into a lethal disease, a process termed antibody-dependent enhancement (ADE). ADE therefore represents the key challenge for developing a safe and effective dengue vaccine. Our studies using mouse models of sequential dengue-Zika virus infections have shown that prior dengue immunity confers cross-protection against subsequent infection with Zika virus, suggesting that a universal dengue-Zika vaccine may be effective against all five viruses (i.e., the four dengue serotypes and Zika). Finally, our ongoing studies have revealed that prior dengue immunity also influences the evolution of Zika virus. This finding highlights the capacity of RNA viruses to evade the host immune response and cause emerging and re-emerging infectious diseases of global significance.

Are there human-specific infectious diseases?

Nissi Varki, UC San Diego School of Medicine

Although humans are genetically very similar to the evolutionarily-related nonhuman hominids (chimpanzees, bonobos, gorillas, and orangutans), comparative studies suggest a surprising number of distinctly human differences in the incidence and/or severity of biomedical conditions. Some differences are due to anatomical changes that occurred during human evolution. However, many others cannot be explained either by these changes or by known environmental factors. There are a number of Distinctly Human Diseases and many infectious diseases primarily affect humans, which used to be major causes of death but are less frequent because of sanitation, vaccines, antibiotics, the death rate in humans is now due to cardiac causes or cancer. This talk will provide an overview of distinctly human diseases and then highlight some of histopathological findings observed in a few of the infectious diseases, using also a human-like Cmah null mouse model lacking the CMAH gene (which was lost about 2-3 million years ago in the human population). Examples to be presented include mechanisms whereby Human Influenza A binds and invades human tracheal mucosa specifically, and not other species, and human-specific binding seen with Cholera toxin, Typhoid toxin and Neisseria gonorrhoea.

References:

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Streptococcal molecular mimicry: Pathogenesis, autoimmunity, and vaccines

Victor Nizet, UC San Diego

Group A Streptococcus (GAS) and Group B Streptococcus (GBS) are two of the most important human leading human bacterial pathogens. GAS is the cause of “strep throat”, with 700 million cases per year globally, but also has the potential to produce severe invasive diseases including necrotizing fasciitis (“flesh-eating disease”) and toxic shock syndrome, even in previously healthy individuals. GBS colonizes the lower GI tract and vaginal epithelium in healthy women, but can cause severe infections including sepsis and meningitis in newborn infants. Both bacteria have capsules composed of sugar molecules that resemble sugars naturally present in humans. This “wolf in sheep’s clothing disguise” allows the pathogen to hide from the immune system or down-regulate immune cell activity, thereby contributing to their disease potential. GAS also has another sugar molecule in its cell wall that might contribute to cross-reactive immunity involved in the later development of rheumatic heart disease, a major cause of morbidity and mortality in the developing world. This complicates the prospect of vaccine development, but our genetic discoveries may have identified a workaround.

The microbiome and infections of the reproductive tract in human females

Amanda Lewis, UC San Diego

This talk will focus on the human vaginal microbiome and infections of the female reproductive tract. The microbiome plays key roles in human physiology and while understudied, the female reproductive tract is no exception. In women, the vaginal microbiome can fall into one of two categories, broadly speaking. The first is dominated by Lactobacillus, usually *L. crispatus* or *L. iners*. The second is a diverse microbiome containing both a wider variation in species content, as well as an overall larger number of bacteria. The latter, diverse microbiome is often found alongside other indicators of a condition called bacterial vaginosis (BV). This condition is characterized by the presence of exfoliated epithelial cells with attached bacteria, abnormally thin mucus secretions, a sharp amine odor, vaginal pH, and overgrowth of the coccobacillus, Gardnerella vaginalis. BV seems to be part of the spectrum of normal for many women, and evidence from non-human primates seems to suggest that a diverse vaginal microbiome is the ancestral state. The condition is nevertheless associated with a wide range of reproductive health complications that endanger fertility and limit reproductive success. Diverse vaginal microbiotas with Gardnerella as the major member are a unique human feature. Evidence will be presented that Gardnerella can encourage colonization and virulence of other human pathogens and suggest that sialidase could be an important factor.

Salmonella in humans and other animals

Manuela Raffatellu, UC San Diego

Salmonella enterica is a Gram-negative enteric pathogen that is responsible for over 120 million cases of infection world-wide. The species can be divided in six subspecies, and comprise over 2,000 serovars. The vast majority of *Salmonella* serovars can colonize a variety of hosts, including farm animals (chicken, cattle, pigs) that often transmit the infection to humans. A few serovars, however, are restricted to the human host, thus only colonize and infect humans. The first group of serovars are termed “non-typhoidal” *Salmonella* strains and primarily cause gastroenteritis in healthy individuals, although they may cause bacteremia in children, elderly, and immunocompromised patients. The second group of serovars are termed “typhoidal” *Salmonella* and cause typhoid fever, a disease characterized by fever and general malaise, and constipation more often than diarrhea. In my talk, I will give a broad overview of some mechanisms of pathogenicity employed by non-typhoidal and/or typhoidal *Salmonella*, with a focus on the following topics: 1) the mechanisms by which non-typhoidal *Salmonella* causes gastroenteritis; 2) the importance of host immunity in keeping non-typhoidal *Salmonella* localized to the gut; 3) why typhoidal *Salmonella* does not cause inflammatory diarrhea; 4) specific virulence mechanisms of typhoidal *Salmonella*; 5) mechanisms of typhoidal *Salmonella* host restrictions.

Malignant malaria in humans

Elizabeth Winzeler, UC San Diego

Malaria, which is caused by parasitic protozoa and spread by mosquitos, remains a devastating infectious disease that endangers 40% of the world’s population. In 2018, there were almost with almost a quarter billion annual cases and a half million deaths. However, before the discovery of antimalarial treatments, is estimated that, up to 20% of children would have died from malaria, putting strong selective on the human genome. I will discuss how many modern humans carry genetic signatures that reveal a life and death struggle with malaria.

Human adaptive immunity against viral infections

Susan Kaech, Salk Institute

Memory CD8 T cells arise following infection from a heterogeneous population of effector T cells that contains cells of various differentiation states. Many of these effector CD8 T cells develop into end-stage terminal effector cells that die following infection and a smaller portion develops into cells with greater memory cell potential and longevity. Understanding how effector CD8 T cell differentiation is regulated to generate cells of diverse cell fates is important and much progress has been made in identifying several transcriptional factors that regulate effector and memory cell fates, function and phenotypes. And this talk, we will discuss how memory T cells form during infection and are specialized into distinct subsets that maximizes the way in which they provide immunosurveillance throughout the body and long-term protective immunity.