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Innate immune responses against COVID-19 in the elderly and those with underlying conditions

Host Campus: University of California, Irvine
Lead Investigator: Anshu Agrawal

Abstract:
COVID-19 pandemic has affected millions worldwide. Though mild in most cases, a subset of individuals suffer from severe disease that requires hospitalizations and can be fatal. Studies indicate that older individuals and those suffering from underlying diseases such as diabetes, hypertension, heart disease etc. are at higher risk for severe illness from the COVID-19. These individuals are unable mount an effective immune response against the virus to clear it from their body. This leads to increased viral multiplication and pneumonia like symptoms in the lung. Innate immune system cells including dendritic cells and macrophages/monocytes are amongst the first cells to respond to the coronavirus. They produce various protective cytokines that can prevent virus from replicating. In addition, these cells also prime the downstream adaptive immune response including induction of killer T cells that are required to kill the virus. The innate immune response occurs very early within 1-2 days of infection. Emerging data from studies indicates that the killer T cell response is decreased in subjects with severe disease. Data regarding functions of dendritic cells and monocytes in the high risk population is limited. It is difficult to study the response of these cell populations in the COVID-19 infected patients as by the time they are diagnosed with the disease; innate immune response is primarily over. Our hypothesis is that the functions of dendritic cells and monocytes are changed in the high risk individuals rendering them more susceptible to COVID-19. We plan to determine the changes in the functions of these cells in the high risk subjects (elderly and those with underlying conditions) by comparing them to healthy subjects. We hope that the information will help develop therapeutic and preventative measures to protect the vulnerable population.

A Graphene-based Multiplexed Sensor for Ultra-fast and Low-cost COVID-19 Diagnosis and Monitoring

Host Campus: California Institute of Technology
Lead Investigator: Wei Gao

Abstract:
The COVID-19 pandemic is an ongoing global tragedy. Social distancing, self-isolation, and face coverings have been adopted to prevent asymptomatic carriers from infecting vulnerable members of the community. Although widespread COVID-19 infection data would be most effective in evaluating the community spread, there are several bottlenecks to diagnosis and disease detection leading to a backlog of testing and variable results. Standard viral nucleic acid tests are time-consuming and resource-intensive and only identify current carriers. Standard antibody tests are often point-of-care (POC) compatible but do not identify infectious individuals since it is not possible to differentiate between asymptomatic carriers and immune persons. There is thus a need for POC quantitative testing for antibodies and viral products in parallel. We have designed and characterized a novel multiplexed, portable, wireless electrochemical platform for ultra-rapid detection of COVID-19. We plan to measure COVID-19 biomarker concentrations in blood, saliva, and nasopharyngeal swab samples from healthy and infected subjects including viral antigen nucleocapsid protein (NP), COVID-19-specific IgM and IgG antibodies, as well as inflammatory biomarker C-reactive protein (CRP), using immunoassays based on our large-scale mass-producible and low cost laser-engraved graphene (LEG) sensor platform. We demonstrated linear detection in physiological relevant ranges for blood and saliva with a 1-minute sample incubation. Our multiplexed biosensor provides information in these three aspects: early viral infection (NP), infection stage (IgG and IgM), and disease severity (CRP). We present here the next phase of our project in collaboration with The Lundquist Institute / Harbor-UCLA Medical Center as we move towards POC testing with clinical samples. Such a simple POC test that could be conducted at home would help reduce the increasing strain on the healthcare system. Identifying COVID-19 carriers, infected, and immune populations may better inform pandemic containment and mitigation strategies. This project may pave the way for a more accessible and more informative diagnostic tool for COVID-19 capable of automatically capturing test results electronically.

Artificial Intelligence Guided Rapid Repurposing of Therapeutics for COVID-19

Host Campus: University of California, San Diego
Lead Investigator: Pradipta Ghosh

Abstract:
As the rapidly unfolding COVID-19 pandemic claimed its victims around the world, it inspired the Institute for Network Medicine's (iNetMed's) scientists to come up with solutions that are not just going to be impactful in the present but build a roadmap for the future. Phase 1 funding has already helped them overcome two obstacles —First, although generally believed to be a vigorous immune reaction to a viral infection, the physical abnormal response of what makes COVID-19 deadly remains a mystery; we know virtually nothing about what constitutes (nature, extent) or contributes to (cell or origin) such a severe immune reaction. iNetMed's scientists within the Center for Precision Computational Systems Network (PreCSN) have computationally identified an invariant human immune response to respiratory viral pandemics, and validated it in COVID-19, showing its potential to set therapeutic goals and measure therapeutic efficacy in drug screens. Second, to put these insights into actionable next steps, iNetMed's scientists within UC San Diego's HUMANOID Center of Research Excellence (CoRE) have created a human pre-clinical model for viral pandemics. Within a short period of time, and limited resources, they were able to successfully create a human 'lung-in-a-dish' model for emulating the human immune response to COVID-19 and other respiratory viral pandemics. These are now ready to use in experiments that are designed to explore the uncharted territory of COVID-19 and to test the efficacy of drugs for their ability to control viral infection (entry, replication, spread) and the runaway immune system that is seemingly fatal.

The UCSC SARS-CoV-2 Genome Browser

Host Campus: University of California, Santa Cruz
Lead Investigator: Maximilian Haeussler

Abstract:
The UCSC SARS-CoV-2 Genome Browser is a map viewer for the current epidemic's viral genome sequence. The main users of our website are biomedical researchers. They use the website to look up where genes and proteins are located in the genome, they look at DNA probes that are part of commercial diagnostics kits, conservation of a base pair with other viruses and increasingly at mutations of the genome in human viral isolates. Similar to Google Maps, a graphical website like ours helps a lot with locating information. Our website has become a standard tool for researchers working on the almost 1000 times bigger human genomes and increasingly for this viral genome. Without a map viewer, the everyday work with a 40,000bp long genome is more time-consuming. We constantly update our annotation database with new information as it gets published in the scientific literature. Increasingly, positive human nasopharyngeal samples are also sent for sequencing, and by looking at the mutations, one can sometimes get an idea where someone was infected or whether a group of people were infected by the same person or several ones, to study the spread of the disease or ideally even help with contact tracing. To make this easier, we are showing how existing isolates are related, as a tree next to our map. In addition to further updating our data and improving our software to make the display faster for the tens of thousands of samples that will be sequenced across the US, we would like to allow researchers to upload any new genome sequence. We could then place the uploaded sample on our big tree of all other samples. We hope that all the data updates and new features outlined in this proposal will make it easier to study the virus, visualize the tree structure of sequenced virus samples and that this may help with contact tracing later in the pandemic.

A Community Driven Response to Inequities of the COVID-19 Pandemic and Recession

Host Campus: University of California, San Francisco
Lead Investigator: Mindy Hebert-Derouen

Abstract:
The COVID-19 pandemic highlights health inequities experienced by communities of color or low-income—health inequities ultimately generated by persistent structural racism and inequities in the social determinants of health (i.e., economic stability, neighborhood environment, health care, social circumstances, and education). Communities of color in California, including Black, Latinx, and Indigenous communities, have higher COVID-19 infection and death rates. Shelter-in-place guidelines and the pandemic-related economic recession have greater consequences for these communities. Thus, the pandemic and recession will exacerbate health inequities for communities of color or low-income for years to come. We propose a Racial Equity Rapid Response Team to address disparities in COVID-19 risk and worsening social determinants that have resulted from the pandemic and recession. We have three aims. First, we aim to describe on-the-ground conditions among individuals and communities of color or low-income. We will use an innovative mobile health application ("app") to collect real-time data from individuals about their communities in the form of neighborhood reports around what is working or not working for them. Individuals will also respond to surveys about their own circumstances (e.g., employment, food, housing, and well-being). We will analyze neighborhood reports and survey data to describe current conditions among individuals and communities, and changes in conditions over the study period. Our second aim is to develop program and policy to guide local, regional, and state support to individuals and communities. Results from Aim 1 will be combined with data on existing resources (e.g., support services) and population-level data on neighborhoods (e.g., socioeconomic status and demographics) across the state in order to inform programs and policies that support effective resource provision. This evidence-based approach is intended to assure that effective and timely support reaches the people and communities who need it most. Third, we aim to establish a set of measures and data visualization tools for continued monitoring of social determinants of health over time. Thus, our proposed project will empower community-based organizations, foundations, and governments at all levels to provide high priority resources in an equitable and accessible manner.

Longitudinal Surveillance of Health Care Workers to Correlate SARS-CoV-2 Antibodies with Immunity

Host Campus: University of California, Irvine
Lead Investigator: Saahir Khan

Abstract:
The world's response to the COVID-19 pandemic depends on answering the following questions: Who has already been infected? What is the relationship between prior infection and immunity? How long does immunity last? Why do some patients develop severe disease? Measurement of antibodies to the SARS-CoV-2 virus can help answer these questions. However, currently available antibody tests suffer from poor specificity due to cross-reactivity with other human coronaviruses. In addition, while antibodies could potentially neutralize virus and confer immunity, antibodies could also generate a pathologic inflammatory response that worsens severity of subsequent infection. Prior studies measuring SARS-CoV-2 antibodies have relied on tests that can only measure antibody response to a single target and have not followed participants long-term to determine the relationship between antibodies and immunity. A coronavirus antigen microarray was recently developed to measure antibodies against a panel of targets from the SARS-CoV-2 virus. A model has been trained on positive and negative controls to determine the optimal combination of antibody responses that predicts prior SARS-CoV-2 infection with high specificity. A cohort of 1185 health care workers has been recruited, surveyed for occupational and clinical risk factors, and tested for antibodies using this methodology. Preliminary results indicate that 4.5% of health care workers have SARSCoV-2 antibodies predictive of prior infection, and that occupational and clinical factors do not significantly impact this risk.

We now propose to extend this study with follow-up visits at 4 months and 10 months to measure the dynamics of SARS-CoV-2 antibodies in this health care worker cohort over time. At each study visit, health care workers will be surveyed for occupational and clinical risk factors and tested for SARS-CoV-2 antibodies, using both the coronavirus antigen microarray for binding antibodies and live virus neutralization assay for neutralizing antibodies. These health care workers undergo daily symptom and temperature screening with reflex PCR testing for COVID-19, so incidence of infection can be accurately measured in this cohort. We will correlate SARS-CoV-2 antibody responses over time with occupational and clinical risk factors and with clinical immunity and severity of subsequent disease.

Serum amylase and novel multi-omics integration to detect and characterize coagulopathy in COVID-19

Host Campus: University of California, San Diego
Lead Investigator: Erik Kistler

Abstract:
A key insight emerging from the COVID pandemic is the recognition that blood coagulation is severely altered and may be a primary driver of morbidity and mortality. Critically ill COVID+ patients almost universally display an aberrant coagulation profile, indicating a severe disruption of the normal balance between the blood's ability to clot and bleed. The cause of this imbalance is not well understood; however, we believe that the blood coagulation system is compromised by enzymes originating from the bowel. In order to design an effective clinical intervention against these enzymes we must first understand the temporal mechanisms of COVID-induced coagulopathy. Virtually every organ system is affected by the COVID virus, and the gut is no exception. When the gut does not receive sufficient oxygen from the lungs, it becomes "leaky", and allows inflammatory digestive enzymes normally contained in the bowel to enter the bloodstream. Digestive enzymes, if able to access the circulation may break down proteins, including those responsible for maintaining the blood coagulation system. Most gut-derived enzymes are rapidly bound by inhibitors in the blood and are thus difficult to detect. As a result, other gut enzymes such as α-amylase are routinely measured. Amylase is a digestive enzyme that breaks down starches; because it has no inhibitors in the blood it is useful for measuring the extent of digestive enzyme penetration into the circulation. In our preliminary results, elevated amylase levels are significantly associated with mortality in COVID+ patients (44% vs 24%), suggesting a potential role for gut-derived enzymes in the blood. To optimally design and implement a clinical trial inhibiting these enzymes we will first determine the temporal profile of COVID coagulopathy using amylase as a marker for circulating digestive enzymes, incorporating state-of-the-art proteomics, peptidomics, and enzyme activity assays of patient blood, integrated with clinical laboratory values. Results from this study will give a detailed understanding of the coagulopathy and role of bowel-derived enzymes in COVID infection, enabling effective clinical interventions. Our sample population will focus on patients suffering disproportionately from COVID: a majority are Hispanic and have key identified risk factors for COVID infection including obesity, hypertension, and diabetes.

The study and treatment of COVID19-related neurological consequences

Host Campus: University of California, San Diego
Lead Investigator: Alysson Muotri

Abstract:
COVID-19 was rapidly declared a pandemic by the World Health Organization and spread to 216 countries in 5 months, with almost thirteen million cases and more than half a million confirmed deaths worldwide. There are now more than three million confirmed cases in the US, with deaths 137,000 as of July 13, 2020. With no vaccines, approved treatments, and a high infectivity rate, COVID-19 quickly became a public health emergency worldwide, leading to lockdowns in many areas of the world, severely affecting daily life. Early clinical care mainly focused on respiratory illnesses. However, a variety of neurological manifestations in both adults and newborns are also emerging. We will characterize the molecular and cellular alterations caused by the SARS-Cov-2 virus in a human model to understand how it affects the brain. At the same time, we will be testing an FDA-approved drug candidate that blocks viral replication in human brain cells (our preliminary data with seed support) to further validate its efficacy in two in vitro models. Altogether, our data show that our drug candidate can successfully inhibit SARS-Cov-2 viral replication and potentially treat infected individuals. A successful outcome in this proposal will lead to a clinical trial with an already FDA-approved repurposed drug. Moreover, our scalable human model, with robust cellular phenotypes, provides a platform for future large-scale drug screens to prevent viral infection or attenuate subsequent pathological effects during neurodevelopment in infected humans.

Real-Time Population Mental Health Tracking During the COVID-19 Pandemic

Host Campus: University of California, San Diego
Lead Investigator: Alicia Nobles

Abstract:
The goal of this project is to discover the mental health problems facing Americans and Californians following the COVID-19 pandemic. Experts predict that the pandemic will trigger widespread increases in mental health problems, but little data is available to test these predictions. To fill this gap, we turn to tracking internet searches on Google, where the content of a query reflects a mental health problem and their volume reflects the community prevalence. We previously found that internet searches for severe acute anxiety ("panic attack") reached new all-time highs following the outbreak. That study was lauded for being the first to empirically assess how population mental health was potentially impacted by COVID-19 and discuss severe acute anxiety, an outcome overlooked in many opinion pieces on COVID-19's mental health impacts. Extending that work, we will compile thousands of unique queries indicative of mental health problems, mine these trends to (Aim 1) discover the subset with the largest post-outbreak increases thereby identifying and prioritizing the potential mental health problems impacted by COVID-19 and (Aim 2) discover the subset of queries that mirror past survey-based population prevalence of severe psychological distress (SPD) and use those queries to forecast the prevalence of SPD post COVID-19 when survey data are unavailable. Both aims represent the state-of-the-art in using searches for data driven insights (as in Aim 1) and using searches as a proxy for traditional survey-based trends (as in Aim 2). Our study will be the first application of either to mental health outcomes. To make these results actionable, we will compile the product of both aims into a website that runs live on Google search data, allowing investigators, clinicians, and policy makers to monitor population mental health in real-time and strategize resource allocation, develop policy, and provide interventions.

COVID-19 Impacts on Cancer Care Management, Patient Experience and Care Costs

Host Campus: Palo Alto Medical Foundation Research Institute
Lead Investigator: Liang Su-Ying

Abstract:
Due to COVID-19, breast and colorectal cancer screening have dropped by 95%, and 85% respectively, in April 2020, compared to prior years. Public opinion and patient surveys report that nearly one-third of respondents prefer not going to a medical facility and/or experience delay in care. An NCI model estimated that approximately 10,000 excess deaths from breast and colorectal cancer may occur nationally in 2020-2030 due to COVID-related delays in screening and diagnosis.

Using real-world data, the goals of this project are to understand COVID-19's impact on (1) cancer care management, including detection, diagnosis and treatment of cancer, (2) patient-reported experience, and (3) costs of cancer care. Data sources are from electronic health records and patient surveys from Sutter Health, a large healthcare system serving a racially/ethnically diverse patient population in Northern California.

For Aim 1, we will examine the patterns of care (telemedicine use and care disruption/recovery) over time following California's shelter-in-place order and the subphases in the ongoing COVID period. For Aim 2, we will compare whether patient experience (quality of care, access to care, care coordination, and provider communication) differ across patient groups: (a) between pre-COVID and ongoing COVID periods, and (b) between in-person visits and telemedicine visits, both in the ongoing COVID period. For Aim 3, we will examine, with potential delay in care, whether more late-stage cancer cases are diagnosed in the ongoing COVID period, compared to that of the pre-COVID period. We will compare subsequent costs of care between the two periods. In all three Aims, we will examine whether these patterns and impacts of COVID-19 are different by patient characteristics, specifically across race/ethnicity and age.

Sewage Surveillance to monitor COVID19 outbreak

Host Campus: University of California, Irvine
Lead Investigator: Katrine Whiteson

Abstract:
Clues to the spread of the COVID-19 pandemic are flowing from a surprising place. UCI BioSci scientists led by Molecular Biology and Biochemistry Associate Professor Katrine Whiteson, Dr. Jason Rothman and Dr. Theresa Loveless are working to identify the virus SARS-CoV-2 through wastewater. Monitoring sewage provides a glimpse of SARS-CoV-2's diversity and extent without relying on clinical detection or further burdening hospitals or clinics.

Detecting viral diseases this way has precedent: In 2013, a poliovirus outbreak in Israel was first found by examining sewage. More recently, a Dutch team published research in March, 2020 showing SARS-CoV-2 could be detected in wastewater before infected patients were diagnosed. Interest in wastewater based epidemiology has since expanded as a tool for tracking SARS-CoV-2 in communities.

The Whiteson lab worked with sewage samples for several years, with the goal of identifying alternatives to antibiotics by isolating viruses that are active against disease-causing bacteria. As soon as the COVID-19 outbreak began, the group realized they could test sewage to see if SARS-CoV-2 was present, and if so, to what extent. The approach would uncover this crucial information before clinical testing was conducted.

As UCI labs shut-down, Dr. Whiteson and her team shifted to working remotely, and started designing protocols to detect SARS-CoV-2 in wastewater. They brainstormed with others at UCI and nationwide on methods to concentrate the virus, which despite its often-devastating impact appears to be delicate in wastewater. The biggest impediment to the project was obtaining sewage samples during a time when sanitation districts were modifying their operations to concentrate on essential public safety obligations. However, partnerships with the Southern California Coastal Water Research Project and the City of Escondido have given the team an opportunity to try their methods. So far, the team has detected the SARS-CoV-2 virus at all eight Southern California wastewater facilities assayed. During the next year, they propose to survey SARS-CoV-2 genomes from 12-18 samples/week from the same eight wastewater treatment plants. The wastewater surveillance methods being established will be useful for continued monitoring of SARS-CoV-2 evolution, and could be applied to future outbreaks of other human pathogens.

Smoking and COVID-19 onset and severity in a US integrated healthcare delivery system

Host Campus: Kaiser Foundation Research Institute
Lead Investigator: Kelly Young-Wolff

Abstract:
The US is currently responding to the spread of a respiratory illness caused by a novel coronavirus (COVID-19). COVID-19 affects the respiratory tract and can lead to pneumonia, respiratory failure, and death. An emerging body of literature suggests that individuals who smoke or vape may be at increased risk for COVID-19 and its more serious complications. Further, risk for COVID-19 onset and severity associated with smoking or vaping could be higher among vulnerable subsets of patients disproportionately impacted by COVID-19, including racial/ethnic minorities, those with lower socio-economic status, and those with chronic health conditions. However, studies to date have been limited and research is needed to better understand the potential impact of cigarette smoking and nicotine vaping on COVID-19 risk overall and among vulnerable populations. This study uses data from >2.2 million adults from January 1, 2020 to June 30, 2021 who received care in Kaiser Permanente Northern California (KPNC)'s large, integrated healthcare delivery system to test the hypotheses that: 1) current and former smokers and vapers have increased risk of COVID-19 onset and worse disease progression relative to never-smokers, and 2) increased risk associated with smoking or vaping is greater among health disparity populations and those with smoking-related chronic health conditions. The study will yield sorely needed, highly generalizable data to increase understanding of whether smoking and vaping are associated with increased risk of COVID-19 onset and progression. Further, by conducting hypothesis-driven analyses to identify sub-groups of smokers or vapers who may be greatest risk for COVID-19 onset and greater disease severity, results will have immediate public health and clinical implications, providing urgently needed data to inform the design of clinical interventions and aid decision making to blunt the impact of the COVID-19 pandemic among vulnerable populations.