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In This Issue

Letter from the Editor

Our feature this month is an interview with the director of the NIH's National Institute of Environmental Health Sciences (NIEHS), Richard Woychik, Ph.D. Dr. Woychik discusses NIEHS's mission on environmental health and prevention research, including its multiple training opportunities for essential workers during the COVID pandemic. He outlines the institute's efforts to study how climate change, wildfires, and other emerging environmental exposures are affecting respiratory health in major ways. Dr. Woychik also discusses the steps NIEHS is taking to protect and grow the environmental health research workforce pipeline through important priorities set forth in its strategic plan.

The September Quarterly also includes several updates from the NIH, beginning with the appointment of a new director at the National Institute on Nursing Research (NINR) and news of a new NIGMS opportunity in sepsis research. We also include an important description of the ATS's "PhD and Basic Translational Scientists' Working Group", led by Drs. Thomas Mariani and Bethany B. Moore.

Next, we present three commentaries about the conduct of clinical research related to the COVID-19 pandemic:

1. Drs. Ellie Golestanian and Nizar Jarjour from the University of Wisconsin-Madison provide a historical perspective on the conduct of randomized controlled trials and describe their tremendous importance in assessing treatments and vaccines for treating and preventing SARS-CoV-2 infections.
2. Dr. Edward Schenck describes the heroic efforts in the Pulmonary and Critical Care division at Weill Cornell Medicine in New York City to conduct clinical and translational research in patients with COVID during an early surge in the pandemic.
3. Dr. Aartik Sarma describes a new trial, called COMET, designed to study heterogeneity in host responses to SARS-CoV-2 infections, at the University of California-San Francisco.

This edition concludes with a look at current NIH opportunities to enhance the diversity of research trainees, including through the NIH Diversity Supplement Program, written by Drs. Jen Alexander-Brett and Tom Brett at Washington University in St. Louis.

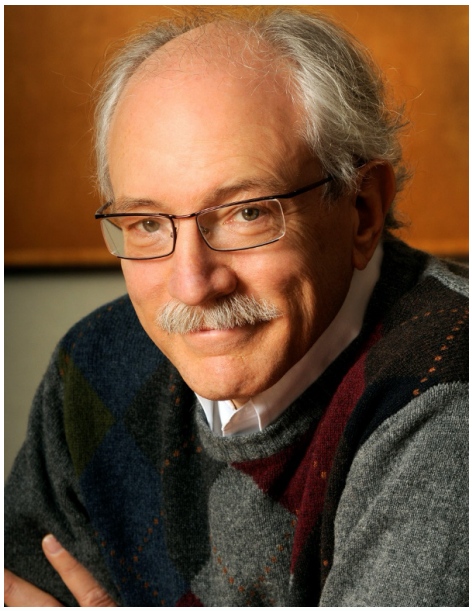
We round out the Quarterly with our report from our Washington Office on health research funding.

Sincerely,

James K. Brown, MD
Editor
Chair, Research Advocacy Committee

RESEARCH NEWS QUARTERLY FEATURE

Interview with NIEHS Director
Richard Woychik, PhD



1. What is your vision for the institute over the next few years?

My vision for leading NIEHS is based on five guiding principles or "pillars" for achieving the noble and ambitious goals laid out in the NIEHS Strategic Plan. These five pillars grew out of my listening sessions with NIEHS staff and stakeholders, combined with my own personal values, experience, and passion for leading this world-class research organization. I am advancing these pillars to help build, with all of you, a shared future vision for the environmental health sciences community. I truly believe that the work supported by NIEHS will provide important insights into the mechanisms of disease that will contribute to both the development of new medical treatments in the coming decade, and better yet, for preventing certain diseases altogether. Our work is more important than ever.

The first pillar is a focus on prevention, which builds on the institute's vision statement to improve public health by preventing disease and disability. Our focus on prevention is also what makes us unique from other NIH institutes, which mostly focus on finding treatments and cures. Our research on hazardous agents within the

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Quarterly Feature: Interview with NIEHS Director *(Continued from page 2)*

environment will help us understand the fundamental mechanisms of toxicity, develop strategies to reduce and mitigate exposures to these harmful agents, and provide individuals and communities with vital information through research translation.

The second pillar is innovation. The NIEHS has a proud history of success based on embracing innovation, but I know that we can do more. It's impossible for us to know where the next transformative idea will emerge, so we need to foster an environment where we reward diversity of thought. Bold new ideas must be embraced and given an equal and fair consideration. We need to embrace the latest and greatest technological advancements from across the biomedical community, and we shouldn't hesitate to develop totally new technologies and approaches, where necessary, to fill the gaps in our current experimental designs. We need to push the concept of high risk-high reward research beyond what we have done in the past. We'll do that by establishing incentives and rewards for innovative thinking.

The third pillar of my vision is collaboration. Environmental exposures play an important role in all diseases and adverse health effects being studied across the NIH. I want to integrate our work on assessing environmental exposures into the fabric of studying the etiology of disease. That's why I will actively seek out collaborations that bring environmental health scientists together with investigators at other institutes and centers across the NIH and with other federal agencies. For example, the new genetics and genomics efforts connected with the Precision Medicine initiatives will likely benefit from collaborations with environmental health scientists studying diseases like asthma, upper respiratory defects, cancer, cardiovascular abnormalities, and a host of other common human diseases. We could even expand this to Precision Environmental Health.

The fourth pillar, and a top priority for me personally, is to build the strongest possible workforce across the environmental health sciences community that embraces the principles of Diversity, Equity, and Inclusion. I believe that NIEHS will remain as the global leader in discovery and innovation only by supporting a pool of highly talented staff from diverse backgrounds. A diverse, creative and highly motivated workforce, with a wide range of skill sets and viewpoints, will keep the environmental health sciences community at the cutting edge of scientific discovery.

The fifth pillar of my vision involves strong leadership at all levels. Working with the global community, we collectively developed the institute's strategic plan, which continues to provide an excellent framework for moving environmental health sciences forward. My focus for the next several years will be dedicated to executing on the strategic plan. As Director of NIEHS, I cannot do this on my own. I am committed to the type of distributed leadership that draws on regular input from scientists and stakeholders from across the environmental health community.

2. At the start of the COVID-19 pandemic, there was some confusion about appropriate PPE for health care providers caring for patients known or suspected of SARS CoV-2 infection. What steps is the institute taking to support both research on the most effective PPE for health workers and training to minimize the risk to front line workers?

The NIEHS Worker Training Program (WTP) COVID-19 Response Training Tool was made available in March 2020, and their training materials were cleared by the White House Coronavirus Taskforce early in 2020. This gave clear guidance on PPE and respirators, based on existing OSHA guidance that says, "An N95 respirator is the minimum level of protection to prevent inhaling coronavirus."

WTP received supplemental funding from Coronavirus Preparedness and Response Supplemental Appropriations Act of 2020 (P.L. 116-123). Through COVID-19-specific supplemental funding to existing annual grants, many WTP grantees are providing training, in English and Spanish, to essential workers across the U.S. and its territories. Additionally, several WTP Small Business Innovation Research Project grants are being used to develop virtual platforms for COVID-19 training.

The NIEHS Superfund Research Program (SRP)-funded researchers at Columbia University who tested a simple method to disinfect and reuse disposable masks in a home oven up to 10 times without decreasing the mask's filter efficiency. Finally, University of Kentucky SRP Center scientists are developing an antiviral membrane mask to capture and deactivate on contact the virus.

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Quarterly Feature: Interview NIEHS Director *(Continued from page 3)*

3. Climate driven forces, like rising heat, changing precipitation patterns, forest fires and super storms, will likely impact the formation and distribution of air pollution. What plans does the Institute have to better understand the links between air pollution, climate change, and human health?

NIEHS provides Time-Sensitive grants to facilitate research response to extreme weather events including wildfires and hurricanes. NIEHS has relaunched an expanded Climate Change and Human Health Literature Portal, a curated knowledge management database of global biomedical and geoscience scientific literature. This database is regularly updated to facilitate awareness and access of the global research community to the state of the science in this area. Publications from 2020 are anticipated to be uploaded to the site in the coming weeks.

4. Would you give some specific examples of ways that NIEHS is supporting investigation of the unique effects of climate change (e.g. environmental temperature changes) on cellular and molecular mechanisms of respiratory diseases?

- Researchers at New York University School of Medicine are investigating the synergistic effects of extreme heat and air pollution, along with obesity, on cardiovascular disease susceptibility.
- Researchers at the University of California at Irvine are using statistical methods to evaluate individual and composite effects of exposure to a mixture of air pollutants while accounting for co-exposure to weather, built environment, and socioeconomic status in a cohort of 400,000 pregnancies.
- Georgia State University researchers are studying ultrafine particulate matter (UFP) and testing the hypothesis that a roadway tree barrier or a tree noise barrier will reduce near-roadway UFP concentration and lead to decreased reactivity in human epithelial cells.
- Research at Louisiana State University A&M College on the myeloid cell-specific role of interleukin 4 receptor alpha (IL4Rα) signaling in mediating ozone-induced inflammation in lung airspaces.

5. The World Health Organization (WHO) recently estimated that environmental exposures contribute to at least 25% of mortality and likely to an even greater fraction of morbidity. Yet, environmental exposures are often over-looked. Besides wildfires and air pollution, what are other current or emerging environmental exposures affecting respiratory health and disease?

Increases in extreme weather events, such as hurricanes and floods, creates an increased risk of exposure to molds and other fungi in homes, schools, and other buildings that poses respiratory health hazards, particularly to children, the elderly, and people with underlying diseases such as asthma. NIEHS continues to fund research to identify and describe these risks. In the aftermath of Hurricane Harvey, researchers at Rice University developed a process and infrastructure for collection of data relating to various environmental exposures of the affected community, including mold in residential and commercial structures.

A post-Hurricane Harvey study by Colorado State University is measuring and characterizing fungal communities found in homes through the use of a Bluetooth-enabled rescue inhaler to identify associations between the exposures and health effects. A study in San Juan, Puerto Rico is coupling molecular and immunological analytical techniques to simultaneously identify indoor fungal microbiota associated with flood damage and airborne pro-inflammatory microbial compounds that contribute to poor respiratory health.

6. Can you describe the NIEHS's research efforts on the health impacts of wildfires, including respiratory illnesses? Also, is the frequency of wildfires impacting biomedical research infrastructure?

NIEHS grantees are investigating the impact of smoke plumes in Nevada from wildfires and prescribed burns. Their research involves measuring and modeling pollutants in these smoke plumes, and then estimating associations of smoke pollutants with maternal, child, and adult acute health outcomes. Their goals are to improve smoke pollutant modeling for public health and to better understand the health impacts of different types of fires.

The NIEHS-funded Bio-Specimen Assessment of Fire Effects (B-SAFE) Pregnancy Study is attempting to find out how wildfires affect the health of pregnant women and their babies. The researchers hope this cohort can be leveraged for future studies of neurodevelopmental and respiratory outcomes in the children born from these wildfire-exposed pregnancies. Researchers will also review common efforts to mitigate those exposures and their effects, such as wearing masks, limiting time outdoors, use of air filtration systems, and re-locating. Along with the B-SAFE study, NIEHS is funding other ongoing research activities involving wildfires with the UC Davis Environmental Health Sciences Center.

NIEHS researchers have found that PM-related adverse health effects attributable to burning biomass represent a crucial public health concern. NIEHS grantees will continue to explore health outcomes from wildfire smoke contaminants including vulnerable populations such as pregnant women and children.

There are certainly many more opportunities for synergistic interactions moving forward. I would like to encourage ATS members to visit our revamped website and take advantage of the extensive knowledge base that can be found there which may be useful to inform clinical care, enhance public health messaging, and craft advocacy campaigns. Our site also offers multiple channels for interacting with us: we always welcome specific concerns, constructive criticism, and topical questions or comments on areas of common interest.

7. Due to COVID, the training and careers of many early career investigators have been disrupted. What steps is NIEHS taking to protect and grow the environmental health research workforce pipeline?

The NIEHS Strategic Plan specifically addresses the research workforce pipeline in Theme Three: Enhancing EHS Through Stewardship and Support. More recently, NIEHS initiated or extended three program announcements to continue training early investigators and their transitioning to the EHS workforce, all under the heading of: Transition to Independent Environmental Health Research (TIEHR). NIEHS supports a variety of mentored and non-mentored career development award programs designed to foster the transition of new investigators to research independence and to support established investigators in achieving specific objectives.

COVID has presented even more challenges beyond those already facing early career investigators. NIH has instituted flexibilities in some programs to help trainees and junior investigators at a time when their universities are closed. For example, NIH has extended the eligibility of K99 applicants for two receipt dates due to disruption in research programs (see https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-158.html.) NIEHS is participating in this announcement with the other NIH institutes. ■

COVID

New HHS COVID Resource

The Department of Health and Human Services, in coordination with NIH, has launched a new web portal called Combat COVID. The site is a user-friendly resource for the public and health providers to get information about COVID, including the different stages of illness, NIH-supported clinical trials and locations to donate blood plasma. The site includes links for people who have never had COVID who are interested in joining a COVID vaccine trial and a link for healthcare providers to obtain more information to guide their patients who have COVID. ■

NIH NEWS

New NINR Director

The National Institute of Nursing Research (NINR) has a new director, Shannon Zenk, Ph.D., MPH, RN, FAAN, who was sworn in on October 14, 2020. Prior to leading NINR, Dr. Zenk was a Nursing Collegiate Professor at the University of Illinois Chicago (UIC) College of Nursing and a fellow at the UIC Institute for Health Research and Policy, where her research focused on social inequities and health. In Dr. Zenk's first Director's Message, she highlighted the critical role that nurses are playing in the COVID-19 response, affirmed the need to continue a research commitment into healthier lives for everyone, and stressed the need to strengthen the nurse scientist workforce. Dr. Zenk also announced that in 2021, NINR will develop its next strategic plan. ■

RESEARCH OPPORTUNITIES

New NIGMS FOA on Sepsis Research

The National Institute of General Medical Sciences (NIGMS) has released a new funding opportunity announcement (FOA) focused on testing current or new biospecimens from sepsis patients. One goal of this FOA is to determine the scientific value of existing or newly collected sepsis human biospecimen sets as testbeds for studies on human sepsis. A related second goal is to provide guidance on the best practices for collecting, utilizing, and analyzing human biospecimens with the aim of maximizing their value for the entire sepsis research community. The FOA invites applicants to submit proof of concept and scale-up studies to determine the scientific value of existing or new collections of human sepsis biospecimens with associated patient health record data.

The open date is January 16, 2021. The title of the funding opportunity is "Exploring the Scientific Value of Existing or New Sepsis Human Biospecimen Collections (R21/R33 - Clinical Trial Not Allowed)" (PAR-21-077).

ATS PhD Group Creates Database of Lung Researchers

By Claude Jourdan Le Saux, Ph.D., Thomas Mariani, Ph.D., & Bethany B. Moore, Ph.D

The Respiratory Structure & Function Assembly is the home of the PhD and Basic and Translational Scientists Working Group, led by Drs. Thomas J. Mariani and Bethany B. Moore. Their objective is to bring together PhD and other basic or translational scientists from across the various assemblies within ATS to discuss ways to enhance the value of ATS membership and the ATS conference for these members. The PhD and Basic and Translational Scientists Working Group advocates for programming,

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PhD Group Creates Database of Lung Researchers *(Continued from page 6)*

policy and recognition of the unique needs of this population within the society.

One of the initiatives of this group is the creation of a database of lung researchers (mostly at the early career level) who are willing and eager to coordinate and deliver virtual seminars for seminar series. Researchers could use this database to populate open slots on divisional or departmental seminar series and to support talented young scientists. Researchers can also add their own name to the database so that they are available to be contacted as well. This is a great way for our ATS community to support ongoing professional development of our junior members and for all of us to learn from the great science going on in these laboratories! The database is found here: Database for Basic and Translational Science Presenters Options (ATS) - Google Docs

ATS MEMBER COMMENTARIES ON CLINICAL RESEARCH RELATED TO COVID-19

Randomized Controlled Trials in the Age of Pandemics

By **Ellie Golestanian, MD, MSc & Nizar Jarjour, MD, ATSF**

Not too long ago, few would have imagined that the phrase "randomized controlled trial" (RCT) would become so familiar to much of the lay public. Those accustomed to RCTs are aware of their importance in the evaluation of potential therapeutics, while others see their complexity as a hurdle in the path of rapid development of new interventions. Both facets have been brought to the forefront since the start of COVID-19 pandemic. Therefore, it is worthwhile to review the role and challenges of RCTs.

For centuries, individual observations or anecdotes constituted the principal mode of learning in medicine. James Lind conducted the first randomized trial in the eighteenth century when he tested citrus fruit as a treatment for scurvy. A few decades later in Boston, Benjamin Waterhouse sponsored a public test of a smallpox vaccine as the disease raged through the city. The pace of advancement accelerated in the twentieth century when treatment options for infectious diseases became more readily available. One turning point came after WWII, when the epidemiologist and biostatistician Austin Bradford-Hill was tasked with establishing the efficacy of streptomycin in tuberculosis. To mitigate against allocation bias, he devised a formal randomization procedure for patient assignment to either treatment or control. His study definitively demonstrated the effectiveness of streptomycin and ushered a new era in medicine.

Aside from assessment of efficacy, trials also determine treatment safety. This was demonstrated most poignantly during the Thalidomide tragedy. Thalidomide, a sedative and anti-emetic, was widely prescribed during pregnancy in Europe, beginning in the late 1950s. Fortunately, the drug was never marketed in the U.S., thanks to the steadfast opposition of Dr. Frances Kelsey, an FDA reviewer at the time. Soon, recognition of its devastating teratogenic effects led to its removal from the market in 1961. That disaster, and the ensuing public outcry led Congress to pass several acts, including the 1962 Drug Amendment Act, designed to regulate the approval and monitoring of new drugs.

The next phase in the evolution of RCTs was set into motion by the AIDS pandemic of the 1980s. At its outset, vast numbers of patients with AIDS were debilitated with a deadly disease without access to, or even the hope of, potentially useful drugs. Here, the FDA came under intense scrutiny for burdensome regulations that excessively slowed drug approvals. The AIDS crisis has been followed in quick succession by SARS-CoV, Ebola and MERS. Now with SARS-CoV-2, we have novel technologies for new vaccines, precisely targeted monoclonal antibodies, as well as new and repurposed therapeutics. The swift pace of progress coupled with an unparalleled speed of communication, near universal use of social media

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Randomized Controlled Trials in the Age of Pandemics (Continued from page 7)

platforms and open access publications facilitated the rapid dissemination of information - from the viral genome to a plethora of global research data. Wide use of these technologies has, however, not been without drawbacks. The instant spread of both true and false information has at times led to a sense of panic and desperation, fueling the urge to forge ahead with therapies, such as Lopinavir-Ritonavir and hydroxychloroquine, that have since been proven ineffective for COVID-19. While clinical reasoning remains an important first step in proffering potential new drugs, it is important that ideas are subjected to rigorous evaluation. As history has taught us, many treatments felt certain to work ultimately proved futile. In patients with severe sepsis, for example, a hypercoagulable state is well recognized. Thus, Activated Protein C was tested, subsequently approved, and marketed, only to be voluntarily withdrawn when further studies failed to show a survival benefit.

Confronted by an infectious disease with high transmission and fatality rates, clinicians must balance the immediate need for therapeutics against the certainty of actual effectiveness and safety. Although most practitioners agree that these assurances are best delivered through RCTs, certain weaknesses of RCTs have been highlighted recently. Chief of these is the perception that they are lengthy, complex, and costly undertakings. Faced with a critically ill patient, should clinicians withhold a potentially beneficial agent outside of a clinical trial? Should strong personal preferences about an agent be put aside for the greater certainty regarding their effectiveness that mainly comes from a properly conducted trials? What about those practicing in small, rural communities who have a low likelihood of being enrolled? What of the rigidity of RCTs in terms of their ability to test more than one agent at a time? There are also criticisms that the process is paternalistic, depriving providers and patients of the autonomy of medical decision-making and applying the art of medicine at the bedside. Proponents of RCTs argue that true benefit cannot confidently be assigned to any agent without the rigors of trial data, lacking which, treatment decisions are made based on personal preferences, and anecdotal 'experience'. At a fundamental level, the debate has remained between the desire for advancement of medical knowledge for the greatest good to the largest number of individuals, and the need to protect the welfare of an individual patient.

To answer some of these criticisms, Adaptive Clinical Trials have been developed over the last two decades. The design of these trials allows testing several interventions in one trial using a shared placebo, and involves ongoing modification based on accrued data. They use Bayesian methodology and computer simulations to detect futility, re-estimate sample size, or preferentially place patients into intervention arms promising greater effectiveness. More complex in their planning and execution, adaptive designs can be established in template forms that are quickly put into place in the event of a pandemic. As new therapies become available, additional arms can be added to such trials, saving time and resources.

Despite some limitations, the impressive success of the RECOVERY Trial of the UK's National Health Service in quickly mounting a large-scale trial during a pandemic is testament to what can be achieved with a comprehensive, coordinated effort. This platform trial, simultaneously evaluating multiple therapies for COVID-19, went from inception to implementation in just two weeks. Importantly, in such trials, even smaller community hospitals can be included. By contrast, as of November 2020, the overwhelming majority (95%) of the 898 clinical trials registered under COVID-19 on ClinicalTrials.gov in the U.S. have too small a sample size to provide actionable data. The absence of a unified national response is compounded by the perceived futility of participation in trials when important candidate agents are quickly granted 'open access', 'compassionate status" or emergency use authorization. While this makes purportedly beneficial treatments more widely available, it represents a lost opportunity to establish the true efficacy of interventions (e.g. convalescent plasma) and the best conditions for their use.

The current pandemic has taught us that despite the many hurdles, we must act swiftly to build the infrastructures necessary for large scale clinical trials in order to provide

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timely, confident answers to clinical care questions. The soon-to-be-available COVID-19 vaccines will hopefully be the light at the end of this dark tunnel. However, we must be prepared for the next pandemic that might confront us in a matter of a few years. The acute need for such readiness relates to the randomness of such events, a fast-changing global climate, and the pressures of rapidly increasing human population density. We hope when the next pandemic happens, we and the rest of the world will be ready.

Clinical and Translational Research During the COVID-19 Pandemic During an Early Surge in New York City

By **Edward J. Schenck, MD, MS**

The COVID-19 pandemic created an unprecedented opportunity to study the heterogeneous host response to a homogeneous pathogen. Due to the susceptibility of the population, the ease of transmissibility and the markedly varied outcomes in COVID-19 there has been a plethora of clinical data. The pace and overwhelming number of infections created an urgency to understand the clinical data and disseminate knowledge in real time. In the very early stages of the pandemic the translational stage was set with publications of the viral genome and in vitro models of disease[1]. Researchers then published early clinical reports about inflammatory patterns, risk factors for progressive respiratory failure, and overall mortality[2]. As the pandemic spread across the globe, the need for further information about the nature of the disease was clear.

In early March 2020, as the first documented cases were being treated in New York City, our Pulmonary and Critical Care Division at Weill Cornell Medicine geared up to manage the pandemic with three aims: 1. to rapidly expand our clinical capability to manage patients with severe respiratory failure; 2. to gather granular, time-dependent patient level data regarding the natural history of severe infections; and 3. to ensure that our patients had access to clinical trials that would increase knowledge regarding the appropriate management of these patients.

As the surge progressed and our hospitals rapidly filled with patients with severe disease, clinical leadership reassigned pulmonary and critical care research staff to lead expanded ICU's and act as consultants to assist our anesthesia, cardiology and pediatric colleagues. I attended in our primary medical intensive care unit, our expanded medical ward-ICUs, and our operating room-ICUs[3]. Through this period, I gained first-hand clinical experience managing critically ill patients with COVID-19 in different practice locations at different stages of the disease.

In order to provide clinical data to understand the disease in near real-time, I worked with a multidisciplinary team including our division of general internal medicine, our research informatics group, and our division of biostatistics and population health. We modified a pre-existing database, the Weill-Cornell Critical Care Database for Advanced Research (CEDAR) that had been designed to capture research-ready data on our ICU population. We updated CEDAR to include data on all mechanically ventilated patients at Weill Cornell Medicine and our partner institutions. Through CEDAR, as well as through manual chart abstraction led by our medical students, we were able to publish several reports about our clinical experience describing patterns of respiratory failure[4] and clinical characteristics of admitted patients[5,6].

These research efforts, along with others from centers throughout the world, were important to establish a framework of understanding related to the clinical syndrome of COVID-19[7,8]. These early reports suffered from several key biases, including limited follow up, causing right censoring of outcomes, and distinct, and likely not generalizable, population characteristics particular to the center generating the data. Despite these biases, we established key COVID-19-related complications, including high rates of renal failure and an increased risk of

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Clinical and Translational Research During the COVID-19 Pandemic During an Early Surge in New York City *(Continued from page 9)*

thromboembolic disease. Some early reports, containing the biases inherent in generating incomplete data from a single center, created confusion regarding the overall prognosis and rates of specific complications[9]. Finding the appropriate balance between generating rapid reports versus delaying to wait for further and more complete data was a daunting challenge[10].

Additionally, population and epidemic variability has made areas of observational data science more challenging than originally anticipated. This includes attempts at predictive modeling and subphenotyping[11]. Predictive modeling, that is creating prognostically robust risk scores for COVID-19 disease outcomes, seemed intuitively simple, as there is only one pathogen. However, early efforts have yielded little beyond descriptive reports[11]. In addition, the variable kinetics of viral spread in the at-risk population speaks to the importance of comparing data across location and time. More specifically, the variability in decisions about who to hospitalize, who to admit to the ICU, and when to treat with mechanical ventilation highlight that clinical care is driven by complex interactions between provider and population dynamics in addition to potentially fixed characteristics inherent to the disease process[13].

To date, there are no obvious clinical sub-phenotypes, or pathophysiologic subtypes, of COVID-19-associated respiratory failure that require novel treatment paradigms beyond best supportive care[14,15]. Characteristics specific to severe COVID-19 in one population may not be present at the same frequency in all populations. Multicenter analyses are the only way to reveal phenotypes that are intrinsic to the disease and stable with respect to varied population dynamics including the Stop-COVID[13]. Further, collaborative large-scale, granular, clinical observational research is needed to explore the temporal, geographic and resource variability in the natural history of COVID-19 in various populations, including Society of Critical Care Medicine's VIRUS-registry and the PETAL network's CORAL studies. If studied at scale, exploring how these population and provider dynamics interact with outcomes in COVID-19 could offer new opportunities. These opportunities include the use of novel strategies to explore causal inference methodologies in the setting of practice and resource and population variation in areas that do not easily lend themselves to clinical trials. Studies based on these methods could also generate hypotheses for future clinical trials.

Beyond clinical sub-phenotyping and modeling, exploring the variability of the host response to a single insult is central to translational research in critical care medicine. The rapid accumulation of moderately sized translational studies highlighting the variability of the host response[16,17] has created a blueprint for novel mechanistic hypotheses to test in therapeutic clinical trials and collaborative observational studies. These translational insights have been garnered from targeted analyses of biomarkers of the innate and adaptive immune response and high dimensional "omics" approaches in both plasma and single cell frameworks. The early scientific experience has demonstrated that many translational techniques have value and may provide insights. However, larger collaborative translational consortia are needed to respond to the true host response variability in COVID-19. Hopefully, lessons learned from this experience will carry forward to the care of patients suffering from respiratory virus infections beyond the current pandemic. ■

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NEW SARS-CoV-2 PHENOTYPING STUDY

Launch of a New Study of Heterogeneity in Host Responses to SARS-CoV-2 Infection: Coronavirus disease 2019 (COVID-19) Multi-Phenotyping for Effective Therapies (COMET)

By **Aartik Sarma, MD**

As we have all learned almost 10 months into the worst global pandemic of the past century, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a heterogeneous spectrum of disease that ranges from asymptomatic infection to critical illness. Since the virus itself does not differ significantly between individuals, variation in outcomes must be driven at least in part by heterogeneity in the host response to infection. Three important questions have emerged regarding the host response: Do variations in early host response mediate susceptibility to severe infection? Can precision therapies modify the immune response to improve outcomes in well-defined subgroups of patients? How is the host response to SARS-CoV-2 distinct from the response to other infections?

To answer these questions, the Coronavirus disease 2019 (COVID-19) Multi-Phenotyping for Effective Therapies (COMET) study is enrolling subjects with SARS-CoV-2 who are admitted to the University of California San Francisco (UCSF) Medical Center or Zuckerberg San Francisco General Hospital. The COMET Consortium includes an interdisciplinary team of over 150 researchers from 16 laboratories and core facilities at UCSF. COMET is part of an international effort to phenotype subjects with SARS-CoV-2. Eligible subjects from COMET are also enrolled in the Immunophenotyping Assessment in

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New Sars-CoV2 Phenotyping Study *(Continued from page 11)*

a COVID-19 Cohort (IMPACC) study, a multicenter study sponsored by NIAID to phenotype hospitalized subjects with COVID-19. Data collection is synchronized with the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) to facilitate future international collaboration.

COMET is collecting serial blood draws and nasopharyngeal swabs and baseline urine samples from patients admitted to the hospital with suspected or confirmed COVID-19, as well as critically ill controls with acute respiratory failure. In addition, tracheal aspirates are collected daily from mechanically ventilated patients. To understand the long-term sequelae and resolution of COVID-19, IMPACC is also collecting blood and nasal swabs at outpatient visits every three months for the first year after subjects are discharged from the hospital. These specimens are being analyzed with a wide array of established sample processing and bioinformatics pipelines that range from single-cell plasma proteomics to tracheal aspirate metatranscriptomics. These large-scale biological data are integrated with a comprehensive clinical data library to study host-pathogen interaction in COVID-19.

As of November 23, 2020, 251 COVID-positive and 62 COVID-negative subjects have been enrolled in COMET. The study population is nearly two-thirds male and over one-half of the subjects identify as Hispanic or Latino, reflecting the demographics of the pandemic in the San Francisco Bay Area. Over 2,500 biospecimens have been collected in this cohort. The first study using data from COMET is now available as a preprint on bioRxiv.[1] Combes et al., performed single-cell RNA sequencing on blood from COMET patients with mild and severe COVID-19 and identified a coordinated pattern of interferon-stimulated gene expression in mild COVID-19 that was not present in severe COVID-19; in contrast, subjects with severe COVID-19 had high anti-SARS-CoV-2 antibody titers and some had auto-antibodies against interferon-stimulated cells. These findings offer a preliminary view of research that can be done in this cohort to understand the role of the host response in SARS-CoV-2.

Results from recent randomized controlled trials in COVID-19 highlight the importance of biological heterogeneity in clinical practice. Dexamethasone decreased mortality in patients who were receiving supplemental oxygen or were mechanically ventilated; however a prespecified subgroup analysis found possible harm in subjects who did not require supplemental oxygen.[2] The mechanisms underlying this pattern are not understood. COMET, IMPACC, and other similar cohorts seek to inform future clinical trials to tailor treatments to selected patients. As severe COVID-19 presents with both sepsis and the acute respiratory distress syndrome, these studies may also shed additional light on phenotypes of these heterogeneous critical illness syndromes. ■

1. Combes, A. J. et al. Global Absence and Targeting of Protective Immune States in Severe COVID-19. bioRxiv 2020.10.28.359935 (2020) doi:10.1101/2020.10.28.359935.
2. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. N Engl J Med NEJMoa2021436 (2020) doi:10.1056/NEJMoa2021436

ENHANCING DIVERSITY AND EQUALITY IN RESEARCH TRAINING

NIH Funding Opportunities to Enhance the Diversity of Research Trainees

By **Jen Alexander-Brett MD, PhD & Tom Brett, PhD**

While the diversity of the scientific workforce has improved over the years, some groups remain under-represented in the biomedical research pipeline. The NIH offers multiple funding mechanisms that aim to support and expand the number of trainees from these groups defined as:

- Racial or ethnic groups including African American, Hispanic or Latino, American Pacific Islander, or Native American/Alaskan Native
- Financially disadvantaged students (Pell grant eligible or equivalent)
- Students with disabilities, defined as those with a physical or mental impairment that substantially limits one or more major life activity

Institution-level programs are available to support undergraduate, post-baccalaureate and graduate-level trainees with emphasis on enhancing diversity. For undergraduates, NIGMS funds research-intensive institutions through the Maximizing Access to Research Careers (MARC) or research-active institutions through the Undergraduate Research Training Initiative for Student Enhancement (U-RISE) T34 programs. A similar cooperative agreement program called BUILD funds students through broader institutional development. Eligible institutions are defined by research intensity criteria based on NIH RPG total costs (MARC U-STAR, U-RISE) and percentage of students supported by Pell grants (BUILD). Currently there are 54 institutions supported by MARC U-STAR, 50 supported by U-RISE, and 10 supported by BUILD, all of which are designed to generate a diverse pool of undergraduates with the skills to successfully transition into graduate programs in biomedical research. In the U-STAR and U-RISE programs, junior and senior undergraduate trainees participate in training activities, learn about career paths and conduct year-round part-time and full-time summer laboratory research. Students supported by these programs are typically provided with an annual or summer stipend and may include partial tuition and fees for up to two years. Post-baccalaureate students can participate in the PREP R25 program at funded research-intensive institutions.

Students in the PREP program hold a recent baccalaureate degree and participate in courses for skill development and a full-time research apprenticeship. Trainees are supported for 1-2 years and the program is designed to prepare recent graduates from under-represented groups to pursue research-focused doctoral degrees. Currently there are 31 funded institutions. Graduate students may be supported by the G-RISE T32 program, which supports pre-doctoral trainees at one of the 50 funded research-active institutions. A list of funded institutions for each of the above programs, including contact information for prospective applicants, can be found on the NIGMS training website listed below.

Programs focused on enhancing the diversity of research participants are also available on an individual basis. Graduate student trainees from under-represented groups may apply for the Ruth L. Kirschstein Predoctoral Individual National Research Service Award parallel F31 program, F31-Diversity, which is intended to enhance the diversity of the biomedical research workforce. Funding deadlines and the application process are the same as the standard F31 program. The award covers annual stipend, tuition costs and institutional allowance and trainees can be supported for up to five years.

The NIH Diversity Supplement Program (DSP) also provides a mechanism for principal investigators with active grants to support a broad range of trainees through the high school to post-doctoral level, including post-baccalaureate and health professional students. Applicable grant types include research, program project,

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center and cooperative agreements (DP, G, P, R, S and U type grants, SCORE or IDeA grants are ineligible). Ideally, these grants should have 1-2 years of funding remaining at the time of application for administrative supplement. Research mentors should make a strong case for how the supplement will benefit the named trainee not currently supported by the parent grant.

Multiple individuals at the high school or undergraduate level may be supported on the same parent grant, though each request must be submitted as an individual application. Support includes salary consistent with institutional policies for high school, undergraduate and post-baccalaureate trainees. Allowable graduate student and post-doctoral stipends are generally in accordance with NRSA funding levels and institutional policies. Typically, awards are provided for two years (but no less than one year) and can be extended up to four years. Applications are evaluated on a rolling basis and generally reviewed in 12 weeks. Well-prepared applications typically have a high success rate but depend on availability of funds and timing related to the fiscal year. For all individual funding mechanisms, prospective applicants are strongly encouraged to contact the Program Officer to discuss eligibility criteria and application instructions. ■

More information including full application instructions can be found at:

https://www.nhlbi.nih.gov/grants-and-training/training-and-career-development/nhlbi-research-supplement-application-guidelines

https://www.nigms.nih.gov/research-training

WASHINGTON UPDATE

Congress Working to Finalize 2021 Spending and COVID Stimulus

During the second week of December 2020, Congress passed a short-term spending measure to give them an additional week to work out an agreement finalizing Fiscal Year (FY) 2021 government spending, which we expect they will do by December 18, 2020. We are cautiously optimistic that NIH is slated for a 2021 funding increase of at least $2 billion, as included in the health spending bill released by the Senate Appropriations Committee. At this point, President Trump has indicated that he will sign the FY2021 spending measure into law.

COVID Relief Legislation

Congress is also working to enact a COVID-19 stimulus bill before the expiration of relief programs for small business and the unemployed at the end of 2020. A bipartisan group of House and Senate members released a $900 billion COVID-19 economic stimulus proposal in early December, primarily as an effort to break the log jam between the more generous House-passed $2.2 trillion HEROES legislation and the $500 billion “skinny” COVID relief proposal favored by Senate Majority Leader McConnell (R-KY). The hope is that this package can ride along with the federal spending legislation referenced above and provide interim relief while a larger, more comprehensive package is worked out in early 2021. The COVID stimulus bill under current negotiation includes $35 billion in relief for health care providers, $6 billion for vaccine development and distribution, $10 billion for COVID-19 testing and contact tracing, and up to $500 million for COVID-related research at NIH. ■