Title: The Era of COVID-19 and the Rise of Science Collectivism in Cancer Research

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TJ reports no conflicts.
DAT reports SAB and stock for Surface Oncology, Leap Therapeutics, and Cygnal Therapeutics, and Mestag. DAT is a co-founder of Mestag. DAT has consulted for Merck, ONO, Pfizer. DAT has performed sponsored research for Fibrogen and ONO.

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Abstract: The coronavirus SARS-CoV-2 has created a global pandemic that has killed more than a quarter million people since December 2019, halted commerce, and disrupted our ability to research cancer in the laboratory and clinic and care for our patients. A return toward a functioning society can be facilitated by the active participation of cancer researchers to diagnose and treat SARS-CoV-2 infected patients, and the direct and indirect benefits of our involvement cannot be overstated.

COVID-19's impact upon our society and cancer research community has been profound. When news of the outbreak emerged during the December 2019 holiday season, it at first did not trigger a decisive global response, perhaps in part because it was seemingly contained and in part because the United States had previously sidestepped SARS and MERS. Now that SARS-CoV-2 has taken a global foothold in humans, it is clear that this RNA virus is highly contagious, oftentimes disabling, and lethal. In patients with confirmed diagnosis, the reported mortality is 7.01% on the day of this writing (Coronavirus Resource Center [https://coronavirus.jhu.edu/]. Johns Hopkins University of Medicine; c2020 [cited 2020 May 6]), although the actual mortality rate is likely much lower, as a larger population of previously infected yet undiagnosed individuals is becoming apparent. Living in the greater New York City area, we witnessed the shocking beginning of this crisis that initially overwhelmed our medical system, with severe shortages of protective clothing and ventilators occurring in an extremely affluent and technologically sophisticated environment. We deeply appreciate the tremendous local leadership and resilient response of health care workers and support staff, first responders, governmental agencies, and charities who rallied together and helped countless patients avoid death from COVID-19. Despite these herculean efforts, sadly, more 26,000 patients have already died of COVID-19 in New York alone (Coronavirus Resource Center [https://coronavirus.jhu.edu/]. Johns Hopkins University of Medicine; c2020 [cited 2020 May 6]), representing more than 34% of the U.S. mortality. COVID-19 has caused our busy world to pause for the last two months, significantly damaging our economy with many citizens staying at home in efforts to isolate the disease and halt its spread. The escalating peak of new admissions for COVID-19 is stabilizing in New York yet still increasing at other locations in the United States, as we now take tentative steps toward reopening certain aspects of the workforce.

COVID-19 has greatly threatened the care of patients with other diseases, and this has been further motivation to researchers and doctors from a diverse range of disciplines to apply their skills to COVID-19. This is especially true for cancer researchers: as a diverse group of disciplines that includes molecular biology, genetics, biochemistry, immunology, chemistry, systems biology, epidemiology and clinical trials, cancer researchers are used to working cooperatively to solve problems, and our skills can be applied to the COVID-19 crisis, with particular attention toward patients with cancer who also suffer from COVID-19. Indeed, cancer researchers are already having a large and positive influence on this pandemic despite the negative effects the pandemic is having upon many in our community, and we will describe a few examples of such efforts. With these examples, we argue that the cancer research community may gain a silver lining as we adopt new approaches in the lab and clinic, and evolve improved methods to collectively solve problems.

To reopen society safely, the importance of rapid and accurate testing for SARS-CoV-22 infection is paramount. Cancer research leaders previously pioneered liquid biopsy approaches as early diagnostic and disease-monitoring methods, and our skills are now being applied to address the problem of identifying SARS-CoV-2–infected individuals. Patients with COVID-19 present across a spectrum, from critically ill patients requiring hospitalization to a larger group of symptomatic individuals who are managed as outpatients. The ideal molecular tests would rapidly and correctly confirm the diagnosis of COVID-19 in patients who present with the classic features of fatigue, fever, headache, dyspnea, and cough, and less commonly anosmia, gastrointestinal complaints, and hypercoagulability syndromes. Furthermore, the urgency for testing is compounded by the realization that a sizable number of asymptomatic SARS-CoV-2 carriers exist (1) who potentially could inadvertently spread the disease to noninfected individuals. However, the severe shortage of tests initially hampered our ability to effectively respond to the COVID-19 pandemic, and even today most FDA-approved tests are limited and cumbersome.

Members of the cancer research community from across the United States have been urgently developing SARS-CoV-2 nucleic acid–based tests that can be routinely applied to the upper respiratory secretions of all individuals so they can safely return to work or gather socially. Recently, processing and amplifying respiratory secretions to detect SARS-CoV-2 was accomplished in a 5-minute viral RNA extraction protocol (2); several rapid approaches have been reported, including CRISPR/Cas RNA recognition–based methods that can detect as few as three SARS-CoV-2 viral genomes in 40 minutes (3), an alternative CRISPR-based proprietary method using SHERLOCK (4), and a reverse transcription–based isothermal amplification protocol that can detect as little as one virion per microliter in 30 minutes (5). One important goal of developing reliable, rapid, and inexpensive diagnostics for SARS-CoV-2 is to screen asymptomatic individuals weekly or even more frequently. The identification of asymptomatic SARS-CoV-2 carriers will confront us with the task of how to properly manage these individuals. Such carriers could be followed in outpatient clinical studies where they would be carefully monitored for potential COVID-19 progression. This will also be an ideal opportunity to study the natural course of disease in patients less severely affected by COVID-19 and to evaluate the ability of potential antiviral therapies to clear SARS-CoV-2 from such individuals. Serological testing to identify individuals with prior or current infection by SARS-CoV-2 is also being evaluated for broad screening across the population in efforts to generate individual risk profiles. Indeed, this would be especially useful if patients can be identified who possess high titers of antibodies which bind to the essential viral epitopes that mediate the attachment of the viral spike protein to its cellular receptor ACE2 (6)—with the hypothesis that such patients may be immune to repeat infections in the near future.

Across the globe, scientists and clinicians have come together to overcome obstacles in researching COVID-19. An example of our personal experience relates to open and continuous brainstorming of the COVID-19 pandemic with several major clinical centers in New York City who were in the epicenter of the pandemic, including Northwell Health, Columbia University, Weil Cornell Medical College, and Mount Sinai School of Medicine It became clear that one hurdle for serological test development was the limited availability of sufficient quantities of SARS-CoV-2 viral spike protein. Fortunately, biochemists with expertise in protein production and structural biology at Cold Spring Harbor Laboratory volunteered to produce these proteins

and collaboratively share them with the academic and corporate biomedical community to facilitate test development. These spike protein preparations can also be applied to the development of neutralizing monoclonal antibodies and convalescent gamma globulin fractions as potential antidotes for critically ill patients with COVID-19.

Medical treatments that interrupt COVID-19 at various stages of disease severity are also needed, and cancer researchers are poised to help. Cancer immunologists have developed and clinically applied methods that either augment or attenuate the immune response, and cancer researchers immediately proposed that late stage COVID-19 activates the cytokine release syndrome (CRS; ref.7). One study reported that patients hospitalized with COVID-19 and CRS responded well to antibodies targeting IL6 (8), and the results of additional studies are eagerly awaited. Patients with CRS may also present with macrophage activation syndrome (MAS), and blockade of the IL1 receptor provided clinical benefits to a cohort of critically ill patients with COVID-19, consistent with the inhibition of MAS (9). An alternative route to block inflammation in COVID-19 using cancer medicines was proposed by several cancer researchers who observed that patients with COVID-19 with Waldenström macroglobulinemia being treated with the Burton tyrosine kinase (BTK) inhibitor ibrutinib had clinical benefits from continued administration of ibrutinib, potentially due to blocking BTK in macrophages (10). In addition to CRS, it has been proposed that patients with advanced COVID-19 may develop aberrant neutrophil activation that results in DNA extravasation termed neutrophil extracellular traps (NET), and that NETs further promote respiratory distress, organ dysfunction, and coagulopathy (11). The search for new treatments for COVID-19 has also attracted the attention of a large group of chemical biologists, biochemists, and cancer researchers who interrogated the proteome of the SARS-CoV-2 and thereby nominated dozens of potential therapies to target this virus (12). Excitingly, these agents are now being quickly tested by other scientists in the world as potential therapies. Besides proposing and testing diagnostic and therapeutic strategies for patients with COVID-19 in the laboratory, the cancer research community can also assist in the evaluation of new investigational agents that target the virus or an abnormal host response by sharing their expertise of evaluating several putative agents in adaptive clinical trials across multiple clinical centers.

COVID-19 affects multiple organ systems, and because cancer researchers routinely integrate their knowledge from the molecular to the organismal level, they are ideally poised to contribute toward deciphering the mechanistic basis for the pathogenesis of this disease. Indeed, cancer researchers have made substantial contributions to our understanding of basic biology by comparing the pathways found in malignancy to those found in normal tissues and inflammation—a precursor condition for multiple cancers that dysregulates tissue homeostasis. A single-cell transcriptomic approach identified the presence of epithelial cell subpopulations in the nose, lungs, and ileum that coexpress the host receptor for SARS-CoV-2 ACE2 and the entry protease TMPRSS2, and furthermore showed that expression of ACE2 could be increased by inflammatory cascades including interferon signaling (13). This work implies that the SARS-CoV-2 target cell population may expand during the initial infection and immune response, providing new susceptible cells to incubate more virus and therefore amplify the severity of the infection in a feed-forward manner. Additionally, small-intestinal organoids were recently used to demonstrate that gut enterocytes may serve as a cellular reservoir for SARS-CoV-2, eliciting strong inflammatory responses during virus spreading in the cultures but without increasing

ACE2 (14). Together, these two reports emphasize the potential importance of pursuing approaches that may alter the host response in efforts to limit the spread of the infection. Finally, pursuing the basis for the increased risk of severe COVID-19 in different ethnic backgrounds could reflect a patient's germline genetics regarding viral infection or host response, the comorbidities of the patient, and/or the environment of the patient, which are the same themes that cancer researchers are avidly exploring to explain health care disparities.

Although some cancer researchers have pivoted their research programs toward understanding and containing COVID-19, many have unfortunately been prevented from doing so as they were sequestered away from their laboratories in efforts to prevent its spread. This has been particularly damaging to trainees, many of whom are dependent upon continuous research productivity. As cancer scientists tentatively return to work, in reduced capacity to maintain social distancing and encumbered by necessary public health precautions, it is hoped that these last two months represent not merely lost time but rather a revolutionary inflection point that will increase productivity by stimulating open cooperation between groups, including those in industry, who were formerly competitors or had limited collaborations because of intellectual property considerations. Perhaps our time engaging with non–cancer experts in the battle against the COVID-19 pandemic may usher in a new type of scientific collectivism where we more openly share ideas and approaches to rapidly develop effective therapies and diagnostics for both COVID-19 and cancer patients. These and related topics will be addressed in a virtual AACR meeting entitled "COVID-19 and Cancer" to be held July 20–22, 2020.

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