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Giacomini, K.M.; Graaf, P.H. van der

The Pandemic as a Catalyst for Disruptive Innovation in Clinical Pharmacology

Kathleen M. Giacomini[1,*] and Piet H. van der Graaf[2,3]

Disruptive innovation, the theme of the 2022 Annual Meeting of the American Society for Clinical Pharmacology & Therapeutics (ASCPT), is a term from business theory that refers to an innovation that challenges larger established markets and creates increased accessibility for the public.[1] Paradigms for disruptive innovation are the personal computer, which disrupted mainframe computers making computers accessible to many, and of course, Wikipedia, which replaced traditional encyclopedias. In biology, disruptive innovation is also a phenomenon, and nowhere has it emerged more rapidly than in the setting of the coronavirus disease 2019 (COVID-19) pandemic. Because of its severity, its rapid spread, and its association with excessively high mortality rates, COVID-19 required the rapid availability of vaccinations, small molecule drugs, and therapeutic antibodies to subvert and treat the disease. Disruption occurred, even in the processes for approving innovations, in order to speed their accessibility to many.

In this issue of *Clinical Pharmacology & Therapeutics* (*CPT*), four papers[2–5] focus on disruptive innovations catalyzed by COVID-19. Two of the four papers describe the use of physiologically-based pharmacokinetic modeling (PBPK), a disruptive computational technology that has fostered the integration of cellular and molecular mechanisms with clinical pharmacokinetics and pharmacodynamics. PBPK models have disrupted the traditional use of trial-and-error methods or extrapolation from mouse to human to predict dose and drug concentrations and have accelerated the timelines for drug development. The models build progressively on our understanding of the molecular processes, including transport and metabolism, that underlie the mechanisms of drug absorption, distribution, and elimination. Walker *et al.*[2] describe the use of PBPK modeling in repurposing studies of the antiparasitic drug nitazoxanide for treatment of COVID-19. The PBPK models suggested that higher than approved doses of nitazoxanide would provide systemic concentrations that conferred antiviral activity against the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) virus. Indeed, based on the PBPK predictions, a phase 1 clinical trial was conducted and indicated that the drug was safe at the higher doses and, importantly, that concentrations that confer antiviral activity were achieved. The drug is now on its way to phase 1b/2a studies in patients with COVID-19 and, if approved, will add to our therapeutic armamentarium of small molecule drugs that can be used to treat patients infected with SARS-CoV-2.

Another disruptive technology has been the development of immunoglobulin G (IgG) monoclonal antibodies (mAbs) engineered against the spike protein of SARS-CoV-2. Complementing small molecule therapies, mAbs to the spike protein have great potential to block viral attachment and entry into human cells. In this case, Chigutsa and coworkers[3] used PBPK models to estimate the

[1]University of California San Francisco, San Francisco, California, USA; [2]Certara, Sheffield, UK; [3]University of Leiden, Leiden, The Netherlands. *Correspondence: Kathleen M. Giacomini (Kathy.giacomini@ucsf.edu)

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doses of the mAb bamlanivimab needed to maintain effective concentrations in lung tissue to neutralize the virus for up to 4 weeks. PBPK modeling provided a disruptive approach to select the first-in-human dose of bamlanivimab that was predicted to yield the maximum therapeutic effect and therefore greatly accelerated the phase I clinical trial by circumventing the extensive use of conventional preclinical and clinical studies to inform dose selection.

The pandemic also placed extraordinary pressure on regulatory authorities around the globe to rapidly approve or authorize the use of therapeutic agents and vaccinations against SARS-CoV-2. Although not disruptive technologies, the emergency authorization approaches used around the world were disruptive processes allowing for the rapid approval of vaccinations, small molecule therapies, and mAbs. In the current issue, Maeda[4] describes the deployment of Japan's Special Approval for Emergency System (SAfE). The system allows for authorization of drugs that have already been approved in other countries and mandates that postmarketing monitoring is conducted to support continued approval of the drugs. The unprecedented pace of approval by Japan's Ministry of Health, Labour, and Welfare of remdesivir, an antiviral drug, and a SARS-CoV-2 vaccine developed by Pfizer and BioNTech is described. Maeda contrasts SAfE with systems in place around the world. In particular, they comment on the Emergency Use Authorization (EUA) system in the United States and rapid authorization systems of the World Health Organization and the United Kingdom. The paper ends with some suggestions of how SAfE can be extended and improved. In particular, the author suggests the removal of the condition that the drug or vaccination has been approved in a foreign country with a rigorous review system.

Disruptive innovations, especially in biology, whether accelerated by a pandemic or other forces, do not occur in a vacuum. Frequently, they are a product of historical discoveries, which are built upon in the innovations. Lalani *et al.*,[5] in their paper entitled "US Taxpayers Heavily Funded the Discovery of COVID-19 Vaccines," describe the role of US taxpayer dollars in supporting the innovations that led to SARS-CoV-2 vaccinations. They begin by describing the initial development and improvement of the disruptive innovation, mRNA vaccinations. The research leading to the mRNA vaccination was supported by more than US $2 million in grants from the National Institutes of Health (NIH). The mRNA vaccination technology ultimately led to the founding of Moderna in 2010 and the further development of mRNA technology, which was used in the rapid development of vaccinations against SARS-CoV-2 infections. BioNTech received US $445 million in funding from the German government, which provided the basis for the Pfizer COVID-19 vaccine.[5] Lalani *et al.* also highlight the fundamental work needed to understand the target for the vaccination, that is, the prefusion spike protein. Over US $8 million was procured from the National Institute of Allergies and Infectious Diseases (NIAID) to support the research of Barney Graham, current deputy director of NIAID Vaccine Research Center, which led to the understanding of the spike protein. Decades of government funding leading to these fundamental discoveries needed for the rapid response to the pandemic were highlighted. Further, Operation Warp Speed spent billions of taxpayer dollars to conduct rigorous clinical trials and manufacturing. Lalani *et al.* ended by pointing out that foundational government funding and funding at each stage of the development and manufacturing of the vaccines places a moral obligation on the United States to end the pandemic sooner. This interesting paper highlights the critical role of the NIH and funding by the US taxpayer in the development and deployment of the disruptive innovations that are needed to end a pandemic.

In the July 2020 *CPT* Editorial, we posed the question whether COVID-19 would be a defining moment for clinical pharmacology.[6] The articles in the current issue of *CPT* (**Figure 1**), consistent with the theme of the 2022 ASCPT Annual Meeting, highlight some of our discipline's technologies, their uses, and the processes and financial support needed to address a pandemic. For example, innovations in computational modeling and simulation clearly disrupted the paradigm of drug development and accelerated clinical trials to address the rapid need for medications in the pandemic. This, coupled with the rapid approval processes institute in the United Kingdom, the United States, Japan, and indeed around the world, helped us meet the challenge of a global pandemic. The costs

Figure 1 *Clinical Pharmacology & Therapeutics* March 2022 cover image: Disruptive Innovations.

for the rapid development and rollout of novel vaccines and treatments were shouldered by many, including US and European taxpayers. Importantly, disruption comes with moral obligations placed on all of us to end the pandemic globally. In addition, according to the original model, a disruptive innovation starts by targeting an overlooked segment, gaining a foothold by delivering more-suitable functionality before moving into other, mainstream, markets.[1] It is not difficult to see how this translates to our world of drug and vaccine development. Last year, DiMasi *et al.* published in this journal that current clinical trial times for infectious diseases range from 2–8 years.[7] We fully support the statement from the recent Editorial[8] in *Nature Medicine* that "Lessons from the rapid development, manufacture and distribution of vaccines against COVID-19 must be broadly applied to expedite vaccine development for other infectious diseases."

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