How Cancer Vaccine Tech Shaped COVID Response

Prior oncology work underpins record-breaking speed of coronavirus drug development

Regulators in the United States, Europe, and elsewhere granted emergency approval in December to the first coronavirus vaccines in the world to demonstrate efficacy in phase III trials, a feat enabled in part by research into anticancer immunotherapies.

The authorized vaccines, BNT162b2 (Pfizer; BioNTech) and mRNA-1273 (Moderna), follow essentially the same blueprint as the companies’ various RNA-based vaccines now in clinical testing for cancer, executives say.

At BioNTech, for example, both the COVID-19 and oncology product portfolios involve RNA that has been sequence-optimized for increased stability and translational efficacy, and lipid-carrier delivery systems designed to reach dendritic cells. The main difference: with BNT162b2, the RNA encodes a viral structural protein, whereas the cancer vaccines express tumor antigens. “In principle, it follows the same idea,” says Ugur Sahin, MD, founder and CEO of the company.

BNT162b2 is not an outlier. Many other COVID-19 vaccine candidates in development—whether built around genetic technologies, viral vectors, or recombinant proteins—feature design elements informed by prior cancer immunotherapy efforts. For many companies, the record-breaking speed of vaccine development in response to the coronavirus outbreak relied heavily on manufacturing infrastructure previously built for oncologic products. Some of the research tools used to guide antigen and epitope selection for anticancer agents have helped in the fight against COVID-19 as well.

Consider viral vector vaccines: A range of poxviruses, adenoviruses, and alphaviruses have formed the basis of cancer vaccines and COVID-19 vaccines alike, with similar prime-boost strategies and the frequent use of non-human-specific viruses to circumvent antiviral immune responses to the vectors.

For example, Vaccitech, a spin-off from the University of Oxford in the UK, had already begun evaluating its replication-deficient chimpanzee adenoviral vector ChAdOx1 in men with prostate cancer before partnering with AstraZeneca on its coronavirus vaccine. The former—a prime-boost combination of ChAdOx1 and a modified vaccinia ankara (MVA) virus, both encoding oncofetal antigen 5T4—proved safe and immunogenic in early testing, with the potential to slash prostate-specific antigen levels when combined with an anti-PD-1 agent (J Immunother Cancer 2020;8:e000928). The latter, a ChAdOx1-only regimen in which the vector expresses the SARS-CoV-2 spike protein, protected against COVID-19 with 70% efficacy in phase III testing (Lancet 2020 Dec 8 [Epub ahead of print]).

According to Don J. Diamond, PhD, of City of Hope in Duarte, CA, reengineering such viral vectors with coronavirus antigens is relatively straightforward. For his MVA-based COVID-19 vaccine candidate, it required simply modifying “plasmids that make up the vaccine virus backbone with SARS-CoV-2 genes using straightforward bacterial genetic methods,” he says (Nat Comm 2020;11:6121). Diamond previously advanced a p53-expressing MVA vaccine for cancer patients into clinical trials, before moving forward with a similar vaccine, now in multiple phase II trials, that encodes antigens from three cytomegalovirus proteins. In November, clinicians at City of Hope began testing his COVID-19 vaccine candidate in healthy volunteers as well.

With an eye to coronavirus vaccines, several research teams have also begun to apply analytic methods first developed to predict which fragments of mutated tumor proteins make the best targets for T-cell recognition and elimination. At Children’s Hospital of Philadelphia in Pennsylvania, for example, John Maris, MD, and Mark Yarmarkovich, PhD, had created algorithms to inform the design of a chimeric antigen receptor T-cell therapy slated to enter human trials in 2022 for pediatric neuroblastoma. Repurposing the tools, they identified a few dozen putative SARS-CoV-2 epitopes that they have begun encoding in DNA- and RNA-based vaccines and evaluating in mice (Cell Reports Medicine 2020;1:100036).

The initial results look “very encouraging,” says Yarmarkovich, noting that his team has observed robust CD4+ and CD8+ T-cell responses and even some neutralizing antibody responses in their animal models.

Not all cancer-to-COVID crossover efforts have gone smoothly, however. When Inovio Pharmaceuticals entered the coronavirus vaccine race, the company, which has a long history of attempting to develop DNA vaccines, deployed an electroporation-based device already used to administer experimental vaccines to patients with various cancers and other infectious diseases. That delivery system, which provides a brief electrical pulse to the skin to enhance plasmid uptake, has been used on thousands of people, but not entirely without issue. In 2016, concerns about the shelf life of disposable parts led to a lengthy delay in the start of phase III trials for Inovio’s lead immunotherapy candidate, VGX-3100, in women with precancerous cervical dysplasia; the drug encodes antigens from two high-risk strains of human papillomavirus.

With the company’s COVID-19 vaccine, FDA officials raised similar questions about a next-generation version of the device, prompting a partial hold on clinical development that took nearly 2 months to resolve.

Aside from conceptual overlaps, and regardless of the platform technology, designing, creating, and testing coronavirus vaccines in a matter of months was made possible by manufacturing capacity already in place for other products, often for oncology. Moderna, for example, cut the ribbon on a $130 million, football field-sized production plant in 2018, with much of the space dedicated to synthesizing and formulating individualized batches of its neoantigen cancer vaccine, mRNA-4157.

Given that product’s personalized nature, and with time of the essence for patients with advanced cancer, “this focus on digital and speed and efficiency in manufacturing actually is a sine qua non of being successful,” says Tal Zaks, MD, PhD, Moderna’s chief medical officer. Now, with much of the company’s COVID-19 vaccine being made under the same roof, the same is proving true of coronavirus vaccines. –Elie Dolgin
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Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-ND2020-018

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